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Bulky nodal disease as distinctive prognosticator in anal cancer management. First Author: Eui Kyo Che, Institute of Radiation Medicine, Medical Research Center, Seoul National University, Seoul, South Korea

**Background:** This study aimed to investigate the prognostic value of bulky nodal involvement in patients with squamous cell carcinoma of anus treated with definitive chemoradiotherapy. **Methods:** Medical records of patients with anal squamous cell carcinoma receiving definitive chemoradiotherapy at three medical centers from 2004 to 2021 were retrospectively analyzed. Exclusion criteria were (1) distant metastasis including non-regional nodal involvement at diagnosis, (2) 2D radiotherapy, and (3) salvage treatment for local relapse. Bulky nodal disease was defined as node with long-diameter 2cm or greater. **Results:** A total of 104 patients were accrued, consisting of 51 patients without, 46 patients with non-bulky, and 7 patients with bulky nodal involvement. Median follow-up duration was 54.0 months (range, 6.4-162.2 months). Estimated progression-free survival (PFS), loco-regional recurrence free survival (LRFS) and overall survival (OS) at 5 years for patients with bulky nodal disease were 42.9%, 42.9%, and 89.4%, respectively. Compared to without or with non-bulky nodal involvement, bulky nodal involvement was significantly related with poor PFS and LRFS. New staging incorporating bulky nodal disease as N2 stage was devised: T1N0-1 as stage I, T3N0-1 as stage II, and N2 as stage III. Estimated PFS, LRFS, and OS at 5 years were as follows: 83.5%, 85.6%, and 91.3%, 60.7% and 93.3%, and 42.9%, 42.9%, and 55.6% for patients with stage I, II, and III disease, respectively (p = 0.0024 for PFS, 0.0015 for LRFS, and 0.28 for OS, respectively). **Conclusions:** Patients with bulky nodal disease receiving standard chemoradiotherapy had poor survival outcomes compared to the other patient groups, suggesting the need for further treatment intensification. Moreover, incorporating bulky nodal disease into the staging system improved the prognostic predictability. Research Sponsor: None.

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**Ezabenlimab (BI 754091) plus modified docetaxel, cisplatin, and 5-fluorouracil (mDCF) followed by chemoradiotherapy (CRT) in patients (pts) with stage III squamous cell anal cancer (SCCA): Early results from the phase II INTERACT-ION study. First Author: Stefano Kim, Department of Medical Oncology, Centre Hospitalier Universitaire de Besançon, Besançon, France; Clinical Investigational Center, CIC-1431, Centre Hospitalier Universitaire de Besançon, Besançon, France; INSERM, Unit 1098, University of Bourgogne Franche-Comté, Besançon, France

**Background:** CRT is the standard of care for locally advanced SCCA. However, up to 50% of pts experience recurrence/definitive colostomy, there is an unmet need for novel treatment (tx) options to improve pt outcomes. mDCF is a standard-first-line Tx for advanced SCCA, and anti-programmed death protein-1 (PD-1) immunotherapy has been shown to be effective in a subset of chemorefractory SCCA. Preclinical and clinical data support the feasibility and the potential of combining mDCF with anti-PD-1 immunotherapy. **Methods:** INTERACT-ION (NCT04719988) is an open-label, single-arm study in pts with Tx-naïve Stage III (T4aN0 or T1aN+ SCCA) to evaluate ezabenlimab (anti-PD-1 antibody) plus mDCF as induction therapy, followed by CRT and then maintenance with ezabenlimab. Pts received induction ezabenlimab (240 mg intravenously, every 3 weeks, 3 cycles) plus mDCF (D [40 mg/m2], C [40 mg/m2] on Day 1; F [120 mg/m2]/day for 2 days) every 4 weeks. If there was no disease progression after 2 months, pts received an additional cycle of ezabenlimab plus 2 cycles of mDCF. Planned early efficacy endpoint analyses were performed after 2 months of Tx. Pts with radiological objective response (OR; RECIST v1.1), pathological complete response (CR)/near CR (<10% viable tumor cells) by repeat biopsy, and molecular CR (undetectable human papillomavirus [HPV] circulating tumor DNA) by liquid biopsy, received nodetumor bed CRT with intensity-modulated radiation therapy (IMRT) followed by 7 cycles of ezabenlimab. All other pts received standard IMRT based-CRT. The primary endpoint is clinical CR rate 10 months after Cycle 1 of ezabenlimab plus mDCF. **Results:** At analysis cut-off date, 43 pts had been enrolled; 37 pts had preliminary early efficacy endpoint evaluation. All but 1 pt (97.3%) received the planned 4 cycles of ezabenlimab plus mDCF plus 2 cycles of mDCF. 6 pts were censored (3 with progression, 1 with death due to acute myocardial infarction, 1 died of suicide, 1 had a adrenal mass, and 1 had a non-progression after cycle 4 of mDCF). 28 pts had treatment-related capillary leak syndrome after Cycle 1 and died of a lung infection 3 months later. Radiological assessment was performed in 33 pts; 32 (97.0%) had radiological CR including 14 (42.4%) with CR. One HPV– pt had disease progression. Pathological response data was available for 21 pts; 16 (76.2%) had pCR or pNCR. For molecular response, 3 pts were HPV– (excluded). Among 23 HPV+ pts, 21 (91.3%) had a molecular CR. Two pts had a significant decrease at 2 months (decrease: 14/1 and 54/1); then molecular CR after radiotherapy. No safety signals were identified by an independent safety review committee. **Conclusions:** Preliminary results from this ongoing Phase II study show promising antitumor activity and manageable safety of ezabenlimab plus 2 cycles of mDCF as induction therapy for locally advanced SCCA. Further evaluation of this new treatment regimen is warranted.

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Oral Abstract Session

Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer. NRG-G1005 (COBRA) phase II/III study. First Author: Van K. Morris, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: For patients (pts) with colon cancer (CC), the detection of circulating tumor DNA (ctDNA) is associated with persistent disease after resection and outperforms traditional clinical and pathological features in prognosticating recurrence risk. We hypothesized that for pts with low-risk stage II CC, a positive ctDNA status after resection may identify pts who benefit from adjuvant chemotherapy. Methods: In this prospective phase II/III clinical trial, pts with resected stage II CC without traditional high risk features and whom the evaluating oncologist deems suitable for active surveillance (i.e., not needing adjuvant chemotherapy) were randomized 1:1 to two arms: standard-of-care/observation (Arm A) or ctDNA assay directed therapy (Arm B). Postoperative blood was analyzed for ctDNA with the Guardant LUNAR assay, covering CC-relevant mutations and CC-specific methylation profiling. Arm B pts with ctDNA detected were treated with 6 mos of adjuvant (CAPOX or FOLFOX) chemotherapy. Primary endpoint for the phase II study was clearance of ctDNA at the 6 mo time-point. A 1-sided Fisher exact test was used to compare ctDNA clearance between Arm A and Arm B among the first 16 pts with ctDNA detected at baseline. If p > .05, the study would be stopped for futility of ctDNA clearance but would otherwise continue to phase III if p ≤ .05. We present the results of the pre-planned phase II analysis. Results: 635 pts were randomized (Arm A: 318; Arm B: 317). One pt with ctDNA detected in Arm B declined protocol-directed chemotherapy but was included in the intention to treat analysis. Among the first 16 pts with ctDNA detected at baseline for the primary endpoint analysis, clearance of ctDNA after 6 mos was observed in 3/7 pts (43%, 95% CI 10.8-82%) in the control arm and in 1/9 pts (11%, 95% CI 0.3-48%) in the experimental arm after chemotherapy (p = .98). There were no unanticipated toxicities in those treated with chemotherapy. Conclusions: The phase II endpoint was not met and further enrollment has been halted based upon pre-specified study stopping rules utilizing the original assay. No improvement in ctDNA clearance was observed after 6 mos of chemotherapy for pts with ctDNA detected following resection of stage II CC. Future trials evaluating ctDNA as an integral biomarker for minimal residual disease determination must account for assay specificity in this pt population. Support: U10CA180868, -180822; U1G1CA189867; Guardant Health. Clinical trial information: NCT04068103. Research Sponsor: NIH; GuardantHealth.

Circling tumor DNA (ctDNA) dynamics in patients with colorectal cancer (CRC) with molecular residual disease: Updated analysis from GALAXY study in the CIRCULATE-JAPAN. First Author: Hiroshi Nakajima, National Cancer Center Hospital Research and Development, National Cancer Center Hospital, Tokyo, Japan

Background: Our previous analysis of data from the prospective, observational GALAXY study (UMIN000039205) reported post surgical detection of molecular residual disease (MRD) to be prognostic of patient (pt) outcomes and the most significant risk factor for recurrence regardless of BRAF V600E status. Here, we present an updated analysis and correlation of ctDNA dynamics in outcomes with pts with radically resected, stage II/IV CRC from the GALAXY study. Methods: A personalized, tumor-informed assay (Signatera, Natera, Inc.) was used for the detection and quantification of ctDNA in serial plasma samples collected at 1, 3, 6, 9, 12, 18, and 24 months post surgery until recurrence. CT scans of chest/abdomen/pelvis were conducted every 6 months. Post-curtative intent surgery, pts underwent either treatment with adjuvant chemotherapy (ACT; N = 1,000) or observation (N = 1,518). The primary endpoint was disease-free survival (DFS), defined as the time between the date of surgery and date of detection of relapse/death due to any cause. Results: Of the 3,034 CRC pts enrolled between May 2020 and November 2022 in the GALAXY study, 2,518 pts met the inclusion criteria and were analyzed in this substudy. The median follow-up was 16.3 months (range 0.1-37 mos). During the post-op MRD window, ctDNA results were available for 2,093 pts (309 (14.8%) of whom were ctDNA+ and 1,784 (85.2%) were ctDNA-. Pts who were ctDNA+ during the MRD window (MRD+) had a significantly inferior DFS compared to MRD- pts (HR: 1.55, 95% CI: 1.29-1.86, p < .0001). Within the MRD+ group, a landmark analysis of ctDNA dynamics from MRD detection to 3-month time point revealed that pts who remained ctDNA+ were over 5 times more likely to recur compared to those who had cleared ctDNA (HR: 5.4, 95% CI: 3.58-7.67, p < .0001). Among the 309 MRD+ pts, 193 (62.2%) received adjuvant therapy (ACT+), 72.9% (132/181) of whom had ctDNA clearance. Notably, for those pts with subsequent ctDNA time points available, 68/126 (54%) had sustained clearance vs. 58/126 (46%) pts eventually returned ctDNA+. Pts with sustained clearance had remarkably better outcomes compared to those with transient ctDNA clearance (HR: 32.57, 95% CI: 9.24-106.16, p < .0001). Furthermore, we observed that among MRD+ pts treated with ACT, a 50% or greater decrease in ctDNA levels (mean tumor molecules/mL) at 6 months was associated with better DFS compared to pts with <50% decrease or increase in ctDNA levels (HR: 2.39, 95% CI: 1.32-4.34, p = .004). Conclusions: ctDNA-based detection of MRD as well as ctDNA dynamics in response to ACT were highly prognostic of pt outcomes. Ongoing randomized VEGA and ALTAIR studies in the CIRCULATE-JAPAN will establish clinical utility of ctDNA-guided adjuvant treatment. Clinical trial information: UMIN000039205. Research Sponsor: Japan Agency for Medical Research and Development.

Oral Abstract Session

Organ-preservation in rectal cancer: What is at risk when offering watch and wait for a clinical complete response? Data from 2 international registries in rectal cancer. First Author: Laura Melina Fernandez, Champalamaud Foundation, Lisbon, Portugal

Background: Organ-preserving surgery has become an attractive alternative to total mesorectal excision (TME) for some patients with rectal cancer following neoadjuvant therapy. Patients who achieve a complete clinical response (cCR) are currently offered watch-and-wait (WW) without immediate resection. Nearly 30% of these patients will develop local regrowth usually within 3 years from initial decision to WW. While salvage resection is frequently managed by TME at time of reassessment of response. Leaving the primary undetectable tumor in situ until development of local regrowth may result in worse oncological outcomes. Future studies incorporating organ-preservation strategies should focus on the subsequent risk of DM among patients who eventually develop local regrowth as one of clinically relevant primary endpoints. Research Sponsor: None.

Effect of laparoscopy-assisted vs open surgery on 3-year disease-free survival in patients with low rectal cancer: The LASRE randomized clinical trial. First Author: Pan Chi, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Background: Laparoscopic surgery has been increasingly used for low rectal cancer due to long-term benefits versus open surgery, but the long-term oncologic outcomes have not been fully established. Methods: This is a multicenter, noninferiority trial. Surgeons who had completed ≥ 100 laparoscopic TME surgeries from 22 high-volume centers in China participated in this trial. A total of 1070 patients scheduled for curative-intent resection of low rectal cancer (lower margin < 5.0 cm dentate line) were randomized at a 2:1 ratio to undergo laparoscopic or open surgery from November 2013 to June 2018. The primary outcome was 3-year DFS; the noninferiority margin was 10% in the modified intent-to-treat population. Secondary outcomes included 3-year overall survival (OS) and locoregional recurrence. Results: The final analysis included 1039 patients (median age: 57 years, 620 men; 685 and 354 in laparoscopic and open groups, respectively). Clinical TNM stage was II/III in 659 patients, and I in the remaining 380 patients. The 3-year DFS rate was 81.4% in the laparoscopic group versus 79.8% in the open group (HR, 0.9 [95% CI, 0.7 to 1.2]; log-rank P = .558). The absolute difference was 1.6% (1-sided 97.5% CI, -3.34% to +5.3%, log-rank P = .243). The 3-year locoregional recurrence rate was 3.8% and 2.4% (respectively, 95% CI: -1.07% to 3.45%, log-rank P = .209). Results of the per-protocol and as-treated analysis were consistent with the main analysis. Conclusions: Among patients with low rectal cancer, laparoscopic surgery performed by experienced surgeons is not inferior to open surgery concerning 3-year disease-free survival. These results support laparoscopic surgery as a safe, minimally invasive approach for low rectal cancer. Clinical trial information: NCT01899547. Research Sponsor: the Key Clinical Specialty Discipline Construction Program of the National Health and Family Planning Commission of China, the Minimally Invasive Medical Center Construction Program from the Fujian Province of China; Joint Funds for the Innovation of Science and Technology, Fujian Province.

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Circulating tumor DNA (ctDNA) for informing adjuvant chemotherapy (ACT) in stage II/III colorectal cancer (CRC): Interim analysis of BESPOKE CRC study. First Author: Paschalis Moutsouris Kazi, Weill Cornell Medicine, New York University School of Medicine. New York, NY.

**Background:** ctDNA-based post-surgical detection of molecular residual disease (MRD) is known to be predictive of a high risk of recurrence. Here, we report the first results of BESPOKE CRC, a multicenter, prospective, observational study evaluating the ability of a tumor-informed ctDNA assay to inform ACT treatment decisions in stage II/III CRC patients (pts).

**Methods:** Of the 1792 pts enrolled between 2020-07-02 and 2022-08-23, plasma ctDNA samples from the first 350 pts with stage II/III CRC were analyzed. ctDNA was detected and quantified using a personalized, tumor-informed assay (Signatera, Natera, Inc.). Following curationative resection, 232 pts received ACT and 118 underwent observation. **Results:** The co-primary endpoints (P-stage II CRC pts; the median follow-up was 24.8 months). ctDNA results at the post-op MRD time point (tp) were available for 295 pts; 15.6% (46/295); stage II: 9/130=6.9%; stage III: 37/165=22.4% of pts were ctDNA positive (ctDNA+ at MRD tp (MRD+)). MRD positivity was significantly associated with inferior disease-free survival (DFS) in stages II-III combined (HR=20.8, 95% CI: 10.0-43.4, p<0.0001) and in stage-stratified subgroup (stage II: HR=22.5, 95% CI 6.8-79.3, stage III: HR=18.1, 95% CI 7.3-45.1). Within the MRD+ group, pts receiving ACT had longer DFS compared to those in the observation group (median DFS: 18.7 vs 6.7 months; HR=3.9, 95% CI: 1.3-11.5, p<0.001). In contrast, there was no benefit of ACT observed in MRD- pts (HR=1.1, 95% CI: 0.3-3.9, p=0.80). Of the MRD+ pts, 99.1% (18/46) had ctDNA detected at 12-weeks post-surgery. Pts with ctDNA clearance had longer DFS compared to those who remained positive (median DFS: 24.2 vs 13.8 months; HR=0.4, 95% CI 0.1-1.0, p=0.045), however, there was no benefit of DFS that were ctDNA- at both 4- and 12-weeks (HR=22.5, 95% CI 6.8-75.9, p<0.0001). Notably, 44.4% (81/185) of pts with ctDNA clearance underwent 8 cycles of FOLFOX chemotherapy. No difference in radiological detection of relapse. ctDNA results during surveillance were available for 339 pts, of whom 8.3% (59/339) were ctDNA+ and had significantly worse DFS compared to serendipitously-detected ctDNA+ pts (HR=124.3, 95% CI 29.8-518.7, p<0.0001).

**Conclusions:** ctDNA-based MRD detection of MRD was highly prognostic of recurrence in an early representative subset of BESPOKE CRC cohort. Data from the expanded cohort will be presented at the meeting.
Rapid Oral Abstract Session

Refining first-line treatment decision in RAS wildtype (RAS-WT) metastatic colorectal cancer (mCRC) by combining clinical biomarkers: Results of the randomized phase 3 trial FIRE-3 (AIO KRK0306). First Author: Julia Walter Holch, Department of Medicine III and Comprehensive Cancer Center, University Hospital, LMU Munich and German Cancer Consortium (DKTK), Partner Site Munich and German Cancer Research Centre (DKFZ), Munich, Germany

Background: Optimal patient selection for first-line treatment targeting epithelial growth factor receptor (EGFR) in RAS-WT mCRC is based on primary tumor sidedness (PTS) with anti-EGFR being the preferred option for patients with left-sided mCRC (LC). Right-sided mCRCs (RC) are preferentially treated in combination with bevacizumab targeting vascular endothelial growth factor (VEGF). Here, improvement in patient selection was evaluated by combining clinical biomarkers beyond PTS using the randomized phase III trial FIRE-3. Methods: FIRE-3 evaluated first-line FOLFIRI (folinic acid, fluorouracil and irinotecan) plus cetuximab (FOLFIRI/Cet) versus FOLFIRI/Bev with bevacizumab (FOLFIRI/Bev) in patients with RAS-WT mCRC. Besides PTS, further clinical biomarkers were evaluated in pairwise combinations using Cox regression models and model-based recursive partitioning with Weibull models to predict treatment benefit of either treatment arm regarding overall survival (OS); age, sex, liver-related disease status (LDD) and baseline carcinoembryonic antigen serum level (CEA). The resulting P-values of second-order interactions were adjusted using Holm-Bonferroni correction. The model with the best test statistics and P-value was chosen for further evaluations. Results: In 400 patients with RAS-WT mCRC, a model combining PTS and LLD status best predicted treatment outcome of either treatment arm (c-index = 0.603, p=0.005). Here, a significant survival benefit of FOLFIRI/Cet over FOLFIRI/Bev was evident in patients with LC/non-LLD (HR 0.62, p=0.02) compared to LC/LDD (HR 0.82, p=0.40). In patients with RC, FOLFIRI/Bev was significantly associated with OS compared to FOLFIRI/Cet when patients suffered from non-LLD (HR 2.09, p<0.01). However, patients with RC/LLD rather had a benefit from FOLFIRI/Cet compared to FOLFIRI/Bev (HR 0.59, p<0.01). Conclusions: Combining clinical biomarkers PTS and LLD status might improve optimal patient selection for targeted first-line treatment in RAS-WT mCRC. Validation in further data sets is warranted. Clinical trial information: NCT00433927. Research Sponsor: None.

Poster Session

Patterns of presentation and delivery of care of appendiceal neoplasms in the largest municipal health care delivery system in the United States. First Author: Armaan Ahmed, Johns Hopkins University, Baltimore, MD

Background: Appendiceal neoplasms (AN) are rare tumors with a broad spectrum of referral and treatment patterns. NYC Health+Hospital (HHC) is the largest municipal health care system in the United States. Here, we study patterns of presentation and management of AN in this safety-net setting. Methods: We identified 92 patients in HHC with AN between 01/01/2017 to 07/01/2023. Statistical analyses were performed in Python. Results: There were 38 (41.5%) mucinous neoplasms, 24 (26.1%) adenocarcinomas, 23 (25.0%) neuroendocrine, and 7 (7.6%) ex-goblet cell adenocarcinomas. 16 cases of pseudomyxoma peritonei were identified. The median age at diagnosis was 55 (IQR: 45-65). 49% were Hispanic, and African Americans were the largest racial block (28%). 50% of cases presented as appendicities. Appendectomy and a second surgical intervention were more common in this group (p=0.001 and p=0.044, respectively). Other surgical interventions included colon resections and cyrodestruction + Hyperthermic intraperitoneal chemotherapy. Among the patients with mucinous neoplasm or adenocarcinoma, 35 had multidisciplinary tumor board discussion (15 mucinous neoplasm and 20 adenocarcinomas). The median follow-up period was 22.0 months (95% CI: 11.5-30.7 months). Surveillance modalities included CT (75%), EUS (74%) and colonoscopy (35%). 85% remained within HHC during treatment. 16 patients were planned to have chemotherapy, including 9 pseudomyxoma peritonei cases. 5 patients did not follow through, and the other cases had a median of 10 cycles. The following adjuvant chemotherapy regimens were employed: 50% FOLFOX, 20% FOLFIRI, 20% XELODA, and 10% CapeOX and FOLFOX. There were 2 cancer-related deaths (pseudomyxomas). Excluding pseudomyxomas, none had evidence of disease at the last follow-up. Conclusions: Minorities and immigrants constitute the majority of the population of HHC. 50% of AN presented as appendicities emphasizing the need for a robust system to recognize these cases. Despite challenges encountered in providing long-term oncological care, HHC has treated and provided vigorous follow-up for this underserved population. Research Sponsor: None.

15 Poster Session

Validation of a novel web-based application for hepatic arterial infusion fluoroxidinedoxorubicin. First Author: Carleton Scott Ellis, Department of Pharmacy, University of Kentucky HealthCare, Lexington, KY

Background: Hepatic arterial infusion (HAI) fluoroxidine (FUDR) dosing is a complex, multifactorial process with weight-based dosing dependent on the fold change of ascites, amionotransferase, alkaline phosphatase, and total bilirubin relative to reference values from preceding cycles and compounded over time. Given the complexity of dosing calculations and lack of experience with this treatment in community centers, HAI is typically administered only at tertiary oncology centers with limited access for rural disadvantaged patients. We developed an online tool to automate the dosing of FUDR to deliver safe and effective administration of HAI. Methods: The FUDR dosing algorithm developed at Memorial Sloan Kettering Cancer Center was digitalized as eDoseHAI, a novel multi-layer architecture web application tool featuring JavaScript (front-end), CF RESTful API (back-end) and Azure SQL server (data storage with Splunk data lake event registration). To validate this tool, manual dosing from patients who received ≥1 dose of HAI FUDR at our institution 6/2020-8/2022 was retrospectively compared to app-based dosing. Mismatch between app-based dosing and historical manual dosing was designated as dosing errors, excluding intentional adjustments based on physician discretion. Results: Internal validity was tested by entering records into eDoseHAI from 54 patients who received a total of 370 FUDR cycles (median 6, range 1-19). Ten patients (18.5%) were found to have unintentional dosing errors (e.g., delayed dose reductions) during treatment, impacting 52 cycles (14.1%). The median cycle at first error was 3 (range 2-6), impacting a median of 5 cycles (range 3-12). Dosing errors occurred in only 11.1% of the 45 patients supervised by a senior HAI physician, compared to 55.6% of the 9 patients supervised by three less experienced HAI physicians. Dosing accuracy improving over time; among the 14 patients on active HAI therapy, only 1 had an identified dosing error. eDoseHAI was able to reliably and accurately calculate dosing for all patients. Conclusions: HAI FUDR dosing is nuanced and complex, such that dosing errors occurred even with senior HAI oncologists. eDoseHAI is a web-based application tool designed to improve accuracy and thus safety of HAI dosing. The tool facilitates HAI dosing by providing optimal dosing and data feedback from an international HAI consortium, and to conduct a phase II clinical trial in which our team supervises FUDR dosing by community oncologists using eDoseHAI’s supervisory mode with a goal to disseminate HAI therapy to disadvantaged rural patients who lack access. Research Sponsor: None.
Colon cancer screening disparities among limited English proficient patients during implementation of patient navigation services. First Author: Rebecca Yao, Mayo Clinic, Rochester, MN

Background: Age-appropriate colon cancer screening has long demonstrated effectiveness in reducing colon cancer incidence and mortality. However, despite a gradual rise in compliance with colon cancer screening, significant disparities remain, particularly among patients with limited English proficiency (LEP). Multistart stool DNA test (MT-dTNA) testing (Exact Sciences, Madison, WI) has been available over the past decade, but the incidence is increasing in those <50 years of age, early-onset CRC). Studies have examined racial and ethnic differences in CRC incidence in this age group, but little is known about differences in survival. Examining survival by race and ethnicity among patients with early-onset CRC may provide insights about differences in risk factors, access to care, and treatment. Methods: A retrospective cohort study included Kaiser Permanente Northern California health plan members 18-49 years of age and diagnosed with CRC between 2006-2019. Race and ethnicity were self-reported as Asian/Pacific Islander, Black, White Non-Hispanic, and Other. CRC stage was assessed using the Kaplan-Meier method. Results: Of 1620 patients, median age was 45.4 years, 47% were female, 20% were Asian/Pacific Islander, 8% Black, 22% Hispanic, and 50% Non-Hispanic White. Adjusted for age, sex, and comorbidities, White patients had a higher risk of death at 5 years compared to White persons (hazard ratio [HR]: 1.41; 95% confidence interval [CI]: 1.9-1.83) (Table). Sequentially adding annual household income and neighborhood deprivation index had no impact on the association; adding tumor stage decreased the HR to 1.14 (0.87-1.49) and adding tumor and treatment factors decreased the HR to 1.08 (0.82-1.42). Risk of death among Asian/Pacific Islander and Black patients did not differ from White patients. Conclusions: Among insured patients with early-onset CRC, Hispanic patients had a higher risk of death at 5 years than patients of White race. The highest risk was associated with differences in tumor stage at diagnosis, tumor factors, and treatment factors. Targeted interventions to improve CRC symptom awareness and remove barriers to CRC diagnosis and treatment among vulnerable populations may be needed to eliminate disparities in early-onset CRC survival. Research Sponsor: Genentech.

18 Poster Session

Survival by race and ethnicity among insured patients with early-onset colorectal cancer. First Author: Jeffrey Lee, Kaiser Permanente, San Francisco, CA

Background: Colorectal cancer (CRC) incidence and mortality have decreased in the United States since the 1970s, but the incidence is increasing in those <50 years of age, early-onset CRC). Studies have examined racial and ethnic differences in CRC incidence in this age group, but little is known about differences in survival. Examining survival by race and ethnicity among patients with early-onset CRC may provide insights about differences in risk factors, access to care, and treatment. Methods: A retrospective cohort study included Kaiser Permanente Northern California health plan members 18-49 years of age and diagnosed with CRC between 2006-2019. Race and ethnicity were self-reported as Asian/Pacific Islander, Black, White Non-Hispanic, and Other. CRC stage was assessed using the Kaplan-Meier method. Results: Of 1620 patients, median age was 45.4 years, 47% were female, 20% were Asian/Pacific Islander, 8% Black, 22% Hispanic, and 50% Non-Hispanic White. Adjusted for age, sex, and comorbidities, White patients had a higher risk of death at 5 years compared to White persons (hazard ratio [HR]: 1.41; 95% confidence interval [CI]: 1.9-1.83) (Table). Sequentially adding annual household income and neighborhood deprivation index had no impact on the association; adding tumor stage decreased the HR to 1.14 (0.87-1.49) and adding tumor and treatment factors decreased the HR to 1.08 (0.82-1.42). Risk of death among Asian/Pacific Islander and Black patients did not differ from White patients. Conclusions: Among insured patients with early-onset CRC, Hispanic patients had a higher risk of death at 5 years than patients of White race. The highest risk was associated with differences in tumor stage at diagnosis, tumor factors, and treatment factors. Targeted interventions to improve CRC symptom awareness and remove barriers to CRC diagnosis and treatment among vulnerable populations may be needed to eliminate disparities in early-onset CRC survival. Research Sponsor: Genentech.

19 Poster Session

Prevalence and predictors of aspirin/NSAID use among patients with Lynch syndrome (LS). First Author: Sachi Singh, Fox Chase Cancer Center, Philadelphia, PA

Background: LS is among the most common hereditary cancer (CA) syndromes, underpinning 3% cases of colorectal CA (CRC) and 8% CRC. <50 yrs LS. Patients have a high lifetime risk of CA which is lowered by aspirin/NSAID use. Moreover, in LS patients, intestinal and extraintestinal tumors like ASIA and NSIASD have been recognized for their CP benefits, with 35% risk reduction associated with sustained (>2 yrs) ASA use. Existing data are scarce on uptake of CP in LS pts, as well as patient-level factors affecting uptake. Methods: PREVENT-Lynch recruited LS patients in the FoxChase Cancer Center (FCCC) Risk Registry, who were invited to complete a one-time e-survey after providing informed consent (1/2020-6/2020; IRB 20-8104). This survey was additionally provided online (PREVENT-Lynch) to US and international patients through 2 patient advocacy websites (2020/27-2023). Demographic/psychosocial/familial CA history were collected. Perceived inconvenience, side effects, reassurance, and likelihood of recommending available and emerging CA prevention modalities were measured on 5-point (1=low, 5=high) scale. Results: 296 patients with LS completed the survey. Median age was 53 yrs [IQR 44-62] and overall CP use was 37.5%. No significant variation in CP uptake was seen based on race, age, marital status or geographic region (nationally and internationally). Personal history of cancer was reported by 56.4%, but was not associated with CP (p=0.6). Gene mutation contributor to disparity (38%), followed by primary tumor side (10%), and molecular characteristics should be incorporated in multicentric studies of racial survival models. Results: 47,178 patients with CRC diagnosed between 1973 and 2023 with self-reported race was included. 'Identified as Non-Hispanic white (NHW), African American (AA) had worse OS (HR=1.16, P= 1.51-6), while Asians and Hispanics had better OS (HR=0.66, P=4.2E-13 and HR=0.86, P=3.4E-6, respectively). The magnitude of disparity between AA and NHW was greater in metastatic disease (HR=1.2, P=1.7E-4). Among 7,628 patients with clinical molecular diagnosis, five genes differed significantly in mutation frequencies; APC (54% NHW, 62% AA, 57% Hispanics, 46% Asian, FDR=0.01), KRAS (45%, 58%, 50%, 44%, FDR=4.6E-9), PIK3CA (17%, 23%, 17%, 12%, FDR=0.006) were higher in AA, while BRAF (8%, 3%, 4%, 7%, FDR=2.4E-8), KIT (4%, 1%, 2%, 3%, FDR=0.013) were higher in NHW. In multivariate analysis mutations of BRAF (HR= 1.9, P=1.2E-8), KRAS (HR= 1.39, P=1.7E-7), and APC (HR= 0.84, P=5E-4) were significantly associated with OS. Among insured patients, the association; adding tumor stage decreased the HR to 1.14 (0.87-1.49) and adding tumor and treatment factors decreased the HR to 1.08 (0.82-1.42). Risk of death among Asian/Pacific Islander and Black patients did not differ from White patients. Conclusions: Among insured patients with early-onset CRC, Hispanic patients had a higher risk of death at 5 years than patients of White race. The highest risk was associated with differences in tumor stage at diagnosis, tumor factors, and treatment factors. Targeted interventions to improve CRC symptom awareness and remove barriers to CRC diagnosis and treatment among vulnerable populations may be needed to eliminate disparities in early-onset CRC survival. Research Sponsor: Genentech.

20 Poster Session

Understanding causes of racial/ethnic survival disparity in 47,178 patients with colorectal cancer: A quantitative evaluation of molecular, socioeconomic, and clinical covariates. First Author: Mahmoud M.G. Yousef, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: A disparity in overall survival (OS) of colorectal cancer (CRC) patients based on self-reported race has been observed. Separately, differing frequencies of driver gene mutations among racial groups have been observed. The contribution of these molecular differences to disparity in outcomes is not well understood. We conducted a systematic investigation of molecular, socioeconomic (SES) and clinical covariates to quantify the relative contribution of these disparities to survival. Methods: This retrospective platform was used to query electronic health records to identify CRC patients and extract clinical and molecular data. The relative contribution of each variable to OS disparity was determined using mediation analysis consisting of sequential multivariable Cox regression models. Results: 47,178 patients with CRC diagnosed between 1973 and 2023 with self-reported race were included. Identified as Non-Hispanic white (NHW), African American (AA) had worse OS (HR=1.16, P= 1.51-6), while Asians and Hispanics had better OS (HR=0.66, P=4.2E-13 and HR=0.86, P=3.4E-6, respectively). The magnitude of disparity between AA and NHW was greater in metastatic disease (HR=1.2, P=1.7E-4). Among 7,628 patients with clinical molecular diagnosis, five genes differed significantly in mutation frequencies; APC (54% NHW, 62% AA, 57% Hispanics, 46% Asian, FDR=0.01), KRAS (45%, 58%, 50%, 44%, FDR=4.6E-9), PIK3CA (17%, 23%, 17%, 12%, FDR=0.006) were higher in AA, while BRAF (8%, 3%, 4%, 7%, FDR=2.4E-8), KIT (4%, 1%, 2%, 3%, FDR=0.013) were higher in NHW. In multivariate analysis mutations of BRAF (HR= 1.9, P=1.2E-8), KRAS (HR= 1.39, P=1.7E-7), and APC (HR= 0.84, P=5E-4) were significantly associated with OS. Among insured patients, the association; adding tumor stage decreased the HR to 1.14 (0.87-1.49) and adding tumor and treatment factors decreased the HR to 1.08 (0.82-1.42). Risk of death among Asian/Pacific Islander and Black patients did not differ from White patients. Conclusions: Among insured patients with early-onset CRC, Hispanic patients had a higher risk of death at 5 years than patients of White race. The highest risk was associated with differences in tumor stage at diagnosis, tumor factors, and treatment factors. Targeted interventions to improve CRC symptom awareness and remove barriers to CRC diagnosis and treatment among vulnerable populations may be needed to eliminate disparities in early-onset CRC survival. Research Sponsor: Genentech.

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Predicting recurrence using a tumor-uninform ed ctDNA assay detecting MRD in patients with resected stage II or III colorectal cancer: Subset analysis from the GALAXY study in CIRCULATE-Japan. First Author: Yashiaki Nakamura, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

**Background:** The presence of circulating tumor DNA (ctDNA) after curative-intent surgery can identify patients with minimal residual disease (MRD) who are at risk of recurrence and aid with post-surgical risk stratification. ~80% of stage II and only 50% of stage III colorectal cancer (CRC) patients are cured by surgery alone. A tumor-uniformed plasma-only approach for MRD assessment accelerates the turnaround time, enabling rapid adjuvant chemotherapy (ACT) treatment decision making, optimizing the impact on patient outcomes.

**Methods:** A subset of samples from GALAXY, an observational arm of the CIRCULATE-Japan study (UMIN000039295), were analyzed for post-surgical ctDNA detection at a landmark time point (LMT) defined as 4 weeks after curative surgery in pathological stage II or III CRC patients. In a prospective lead-in to clinical validation, 80 patients meeting pre-specified eligibility criteria were randomly selected with enrichment for recurrence to 50% while maintaining the stage II/III recurrence (R)/nonrecurrence (NR) ratio that observed in GALAXY. Residual plasma samples were analyzed with the Temps MX assay (xM), a tumor-uniformed ctDNA MRD assay that integrates methylation and genomic variant MRD classifiers to deliver a binary MRD call. All calls were blinded to clinical outcomes. The methylation-based classifier detects fragments with CRC methylation signatures in differentially methylated regions trained by sequencing CRC and healthy samples on a 6Mbp panel. The variant-based MRD classifier detects highly prevalent CRC variants. Artifacts, CHIP, and germline variant filtering algorithms were also applied.

**Results:** Of the 80 patients (pts), 70 (Stage II/III pts = 29 (41); Stage III pts = 11 (59%)) were evaluable. The concordance rate between MRD by xM and with LMT was followed by ctDNA (xM MRD+) and 30/34 NR pts had undetectable ctDNA (xM MRD−), providing a sensitivity of 50% and specificity of 88%. Additionally, xM MRD+ status strongly correlated with disease-free survival (DFS) with a hazard ratio (HR) of 5.09, adjusted to account for a 24% recurrence rate in GALAXY. In an updated, ongoing longitudinal analysis of the 4 false positive pts, 2 were Stage III, MRD+ from both the methylation and genomic classifiers, received ACT, and have likely cleared their ctDNA without any sign of clinical recurrence. An adjusted sensitivity and specificity analysis resulted in xM clinical performance of 53% (20/38 R) and 94% (30/32 NR), respectively. **Conclusions:** xM is a novel tumor-uniformed assay that demonstrated remarkable performance to detect clinical recurrence at a LMT, and a clinically meaningful correlation with DFS. A larger clinical validation study including longitudinal analysis, correlation with ACT, and outcomes from the GALAXY study is currently underway. Research Sponsor: None.

Association of circulating tumor DNA (ctDNA) molecular disease (MRD) detection with lymph node metastasis after local excision of pathological T1 colorectal cancer: First results from DENEB, a CIRCULATE-Japan Galaxy substudy. First Author: Masaaki Miyo, Department of Surgery, Surgical Oncology and Science, Sapporo Medical University, Sapporo, Japan

**Background:** Patients with pathological T1 (pt1) colorectal cancer (CRC) at high risk for lymph node metastasis (LNM) after complete local resection are recommended to receive additional intestinal resection along with lymph node dissection. However, the existing pathological criteria for risk stratification of LNM are inadequate, such that ~90% of patients without LNM are exposed to potentially unnecessary treatment. Based on the CIRCULATE-Japan platform, we launched DENEB, a prospective substudy within the GALAXY observational study, to explore the ability of predicting LNM using circulating tumor DNA (ctDNA) detection compared to the standard pathological criteria.

**Methods:** This study included patients with pt1 CRC who underwent complete local resection and were scheduled for additional intestinal resection with lymph node dissection based on the standard pathologic risk-stratification criteria for LNM. The additional surgery was indicated for patients meeting any of the following criteria: (1) depth of submucosal invasion (>1000μm); (2) lymphovascular invasion; (3) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; and (4) high-grade tumor budding (BD2/3) at the site of deepest invasion according to the Japanese guideline. ctDNA was analyzed from plasma samples collected within 4 weeks before the additional intestinal resection using a personalized, tumor-informed assay (Signatera bespoke multiplex-PCR NGS assay). The study assessed the diagnostic concordance rate between ctDNA detection and the occurrence of LNM. **Results:** Of 208 CRC patients enrolled between July 2021 and May 2023 in DENEB, 166 patients met the inclusion criteria (79.3%) and were ultimately diagnosed with stage III due to the presence of LNM in additional intestinal resection. Among the 166 patients, 6 patients tested ctDNA-positive; all 6 had LNM, yielding a positive predictive value of 100.0%. On the other hand, 160 patients had ctDNA-negative results, 144 of whom did not have LNM, resulting in a negative predictive value of 90.0%. The overall diagnostic concordance rate for ctDNA in detecting LNM was 90.4% (95% confidence interval, 84.8% to 94.4%). All 6 patients with a ctDNA-positive result and LNM had left-sided colorectal cancer and a tumor diameter greater than 13 mm. **Conclusions:** This analysis showed that ctDNA testing has the potential to improve risk stratification of LNM in patients with pt1 CRC who underwent complete local resection. Clinical trial information: UMIN000039295. Research Sponsor: Japan Agency for Medical Research and Development (AMED); Taiho Pharmaceutical Co., Ltd.
Use of micronuclei DNA from erythrocytes in early-stage colorectal cancer detection. First Author: Xingyun Yao, School of Life Sciences, Westlake University; Institute of Basic Medical Sciences, Westlake Institute for Advanced Study, Hangzhou, China.

**Background:** Current development in stool- and cell-free DNA (ctDNA)-based technologies have demonstrated promising potentials in colorectal cancer (CRC) diagnosis. However, early detection of CRC and advanced adenoma (AA) remains challenging. Micronuclei (MN) are extranuclear bodies containing chromatin segments resulting from errors in DNA repair. Elevated levels of MN+ erythrocytes have been studied in genotoxicity testing and cancer diagnosis. We have developed a method (WJD2021/228246 A1) for purifying and sequencing micronuclei DNA (mnDNA) in erythrocytes from peripheral blood. Here, we compared mnDNA between healthy donors (HDs) and CRC patients and explored its application for early cancer diagnosis. **Methods:** Peripheral blood (10 ml) was obtained from a training cohort of 897 individuals, including 246, and an independent test cohort of 193. mnDNA was isolated and sequenced from erythrocytes. Genome-wide analysis identified distinctive mnDNA features between HD and CRC. Predictive models using these features were developed to differentiate CRC and AA from HDs. A clinical trial comparing mnDNA with an approved multistage stool DNA test (sDNA-FIT) was also conducted on 60 individuals (42 HDs, 6 AAs, and 12 CRCS).

**Results:** Genome-wide analysis of mnDNA revealed substantial differences in distribution patterns between HDs and CRC patients. The predictive model built on mnDNA features achieved an AUC of 92.98% (95% CI: 87.85-98.12%), with an 88.64% sensitivity and 92.75% specificity in the independent test cohort. The model identified early-stage (stage I-II) CRC and AA with sensitivities of 83.33% or 65.65%, respectively. Comparing mnDNA to sDNA-FIT showed superior overall sensitivity (83.33% vs. 61.11%), AA sensitivity (83.33% vs. 16.66%), with comparable specificity (88.10% vs. 85.71%). **Conclusions:** Our results demonstrate that mnDNA from a small amount of peripheral blood enables accurate detection of AA and early-stage CRC. As a type of cytoplasmic DNA, mnDNA can provide a valuable tool for early cancer detection, offering different and complementary mechanism compared to current methods. A larger clinical trial (NCT05875584) is ongoing and will further validate the application of mnDNA in early cancer detection. Research Sponsor: Timing Biotech.

**27 Poster Session**

**INTERCEPT Program of circulating tumor DNA (ctDNA) testing for minimal residual disease (MRD) in colorectal cancer (CRC): Results from a prospective clinical cohort.** First Author: Giulia Maddalena, Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

**Background:** Minimal residual disease, defined by ctDNA in the absence of macroscopic disease, represents a new and clinically poorly defined subset of patients (pts). While observational cohorts have been reported on the prognostic of MRD, there is little information on the impact of retesting and acting on ctDNA results on the subsequent ability to detect radiographic disease. Here we present real-world evidence from a prospective cohort where ctDNA testing was routinely performed and returned to pts and providers, providing opportunities to understand the prognostic performance of ctDNA in practice, including the rate of false negatives defined as radiographic recurrence without detectable ctDNA. **Methods:** The INTERCEPT program enrolled pts undergoing curative intent surgery for stages II-IV CRC at MD Anderson Cancer Center. A tumor-informed MRD assay (Signatera) was drawn post-operatively and every 3 months as per established reimbursement guidelines. Pts enrolled between Jan-Dec 2022 were included with follow up through Aug, 2023. Post-op timepoint was defined as any test within 6.5 months of surgery to include adjuvant therapy. A false negative result was defined as a negative test but with radiographic detection of recurrence within the subsequent 4 months. **Results:** A total of 1,140 pts were included, with 44.7% female and 39% with advanced disease. At least one ctDNA result was obtained in 338 patients (29.6%). When limited to pts with a post-operative/post-adjuvant timepoint (n=520) and a median follow up of 10.4m, the 12m DFS was 94.2% for ctDNA+ and 54.3% for pts with at least 1 ctDNA+ test (median DFS of 14.9m); HR 1.767 (95% CI: 1.08 – 30.99), p<0.0001. When segregated by ctDNA, the median importance of predictors of outcomes (Table), such that pts with stage I-IV ctDNA+ had better prognostic in comparison with stage II ctDNA+ (38.9% vs. 87.7% DFS, p<0.002). For 15 pts, we detected a false negative ctDNA, representing a rate of 1.3% (15/1140) corresponding to a negative predictive value (NPV) of 98.1%. **Conclusions:** In this first prospective real-world ctDNA program, MRD testing using ctDNA NPV (98.1%) with very few false negative cases. The prognostic importance of ctDNA was confirmed and exceeded the risk prediction of stage, alone, underlying the importance of introducing the test in practice and the need to investigate interventional studies, as are ongoing in the INTERCEPT program (ctDNA.org). Research Sponsor: None.

**28 Poster Session**

**Diagnostic performance of endoscopy and MRI in identifying true response among patients with rectal cancer treated with total neoadjuvant therapy and selective watch and wait or TME.** First Author: Dana Mohamed Rashid Omer, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

**Background:** The success of a watch-and-wait (WW) strategy for rectal cancer relies on restaging endoscopy and MRI to correctly identify a true response (TR) to neoadjuvant therapy. This secondary analysis of the OPRA trial is the first study to evaluate the restaging assessment’s diagnostic performance in a large cohort of WW patients. **Methods:** In the OPRA trial, patients with stage III/II rectal cancer were treated with total neoadjuvant therapy (TNT) and restaged with endoscopy and MRI 8-10 weeks post-treatment. Patients with a clinical complete (cCR) or near complete (cCR) response were offered WW; patients with an incomplete clinical response were recommended for total mesorectal excision. Diagnostic parameters, including accuracy, sensitivity, specificity, positive and negative predictive values, were calculated using TR as the reference standard. **Conclusions:** Positive posttest probability that a patient with a cCR had a TR was 81%, while the negative posttest probability that a patient with a non-cCR had a TR was 30%. Significance: Restaging endoscopy outperforms MRI in predicting TR, but the assessment’s overall accuracy even when both tests are combined remains suboptimal. Our results highlight the challenge of recognizing TR using subjective restaging exams. Opportunities to improve diagnostic accuracy include machine learning and radiomics, which have the potential to aid clinicians in identifying true responders. Research Sponsor: None.

**Diagnostic performance identifying a true response (TR) for patients with a cCR or nCR (Panel A) and patients with cCR only (Panel B).**

<table>
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<th>Parameter</th>
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<td>Negative predictive value</td>
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<td>Negative PTP</td>
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TPT*: posttest probability.
Disparities and trends in biomarker testing in metastatic colorectal cancer.

First Author: Michael H. Storandt, Mayo Clinic, Rochester, MN

Background: Incidence of early-onset colorectal cancer (eCRC) (~50 years of age) is increasing globally. However, little is known regarding symptom burden in this sub-population. We compared symptoms in patients with eCRC to those of patients with average-onset CRC (aCRC, diagnosed at age ≥ 50). Methods: eCRC is a stepped-wedge, parallel-arm, randomized clinical trial evaluating a collaborative care model for the assessment and management of symptoms in patients with early-onset colorectal cancer (eoCRC). Methods: Patients with eoCRC enrolled prospectively and were assessed for commonly reported symptoms occurring symptoms are associated with specific symptoms in this population. Research Sponsor: None.

Poster Session

31

Symptom burden in patients with early-onset colorectal cancer: A subgroup analysis of the enhanced, EHR-facilitated cancer symptom control (E2C2) trial. First Author: Michael H. Storandt, Mayo Clinic, Rochester, MN

Background: Incidence of early-onset colorectal cancer (eCRC), ~50 years of age) is increasing globally. However, little is known regarding symptom burden in this sub-population. We compared symptoms in patients with eCRC to those of patients with average-onset CRC (aCRC, diagnosed at age ≥ 50). Methods: eCRC is a stepped-wedge, parallel-arm, randomized clinical trial evaluating a collaborative care model for the assessment and management of symptoms in patients with early-onset colorectal cancer (eoCRC). Results: Symptoms in eoCRC were more severe compared to aCRC. Patients with eoCRC reported higher symptom severity than patients with aCRC. This suggests unique needs for symptom management in patients with eCRC. Additional research is needed to evaluate how time since diagnosis, disease characteristics, cancer-directed treatment patterns, and co-occurring symptoms are associated with specific symptoms in this population. Research Sponsor: None.

Applying the fragility index to randomized controlled trials evaluating total neoadjuvant therapy for rectal cancer. First Author: Tyler McKechnie, McMaster University, Hamilton, ON, Canada

Background: A relatively novel summary measure that is not commonly reported in randomized controlled trials (RCTs) is the fragility index (FI). This describes the number of trials (p-values) that would have to be lost to lose statistical significance (p > 0.05). As such, we proposed applying the FI to a number of medical subspecialties such as critical care, orthopedic surgery and colorectal surgery. Recently, there has been significant interest in, and adoption of, total neoadjuvant therapy (TNT) for locally advanced rectal cancer (LARC). The FI has been applied to the robustness of TNT in LARC. We manually searched Google Scholar and PubMed to identify any other relevant RCTs. Outcomes within these RCTs that were either dichotomous outcomes or time to event outcomes were eligible for inclusion if the reported effect size had an associated p-value of less than 0.05. The main outcome was the FI for each statistically significant outcome. Walsh et al.’s method of calculating FI was utilized. A RCTs results were considered fragile if the FI was less than the loss to follow up for a given outcome. Correlations between FI and research characteristics were assessed using the Spearman’s rank correlation coefficients. Results: Ten RCTs were identified with 25 outcomes having statistically significant differences between groups (p-values < 0.05). Eleven outcomes were time-to-event outcomes, while the remainder were dichotomous outcomes. About half (n=13) were oncologic outcomes (i.e., survival, recurrence), while the rest (n=9) were long-term complications. The median FI was 2 (interquartile range [IQR] 1–16). The number of patients lost to follow-up exceeded the FI in 17 outcomes (68.0%) and thus these results were considered “fragile”. Lower FI was associated with high risk of bias (rho=-0.5594) and higher loss to follow-up (i.e., greater than 5% vs. less than 5%) (rho=-0.4394), while higher FI was associated with large sample size (i.e., greater than 500 patients) (rho=0.3578). Conclusions: The robustness of outcomes from trials assessing TNT for LARC was found to be questionable. Most of these outcomes were fragile, as determined by the FI. In most cases, two or less additional events would have resulted in a loss of statistical significance of the reported results. Those using the results of these studies, including clinicians and health policy experts, should apply caution when interpreting these types of trials. Research Sponsor: None.
Outcomes of elderly patients with node-positive colon cancer: A multicenter population-based cohort study. First Author: Carl Pinter, University of Saskatchewan, Saskatoon, SK, Canada

Background: Patients with stage III colon cancer are at high risk of recurrent disease. In this large population-based cohort study we examined prognostic significance of chemotherapy and other clinical, pathological & contextual variables that are associated with inferior outcomes in elderly patients with stage III colon cancer. Methods: Patients ≥70 years with stage III colon cancer diagnosed in Saskatchewan, a Canadian province, and underwent resection of the primary tumor during 2012-2018 were evaluated. A Cox proportional multivariate survival analysis was performed to determine factors correlated with overall survival (OS) and disease-free survival (DFS). Results: 404 eligible patients with median age of 79 yrs & M/F of 1:1 were identified, 48% were ≥80 yrs, 60% were rural resident, 66% had >1 major comorbid illness, 34% had WHO performance status ≥2, 44% had an ostomy formation, 46% had a T4 or N2 high-risk disease, and 50% had positive node harvested (NPNH) ratio >0.1. 43% patients received adjuvant chemotherapy. Median time to start chemo was 9 weeks. Patients who did not receive adjuvant chemotherapy were significantly older, had low performance status or experienced high rate of post-operative morbidity, high serum creatinine, low albumin, anaemia, elevated WBC count and platelets. Median OS of all patients was 51 months (95%CI: 42.5-59.6), with estimated 5 & 10-yr OS of 45% and 30%. Median DFS of entire cohort was 32 months (26.3-37.7) with 5 & 10-yr DFS of 34% and 20%. Patients who received adjuvant chemotherapy had median OS of 106 months (83.8-128.5) vs. 30 months (23.4-36.0), p<0.001 with 5 & 10-yr OS of 64% and 49% vs. 31% and 19% (p<0.001). Patients who received adjuvant chemotherapy had median DFS of 56 months (28.2-83.9) vs. 22 months (16.5-27.5), p<0.001 with 5 & 10-yr DFS of was 49% and 30% vs. 24% and 13% (p<0.001). The Cox-multivariate analysis revealed a past history of cancer, HR, 1.1, (1.0-1.2), osyrosis, HR, 1.3, (1.0-1.7), high-risk disease, HR, 1.5, (1.2-1.9), T3/T4 tumor, HR, 1.5, (1.3-1.8); WHO performance status >1, HR, 1.3, (1.0-1.6); no adjuvant chemotherapy, HR, 1.3, (1.0-1.8); high-risk stage III disease, HR, 1.3, (1.1-1.9); and baseline CEA >5, HR, 1.5, (1.3-2.2), were independently correlated with DFS whereas past history of cancer, HR, 1.4, (1.1-1.9); high-risk stage III disease, HR, 1.6, (1.2-2.2); and CEA >5, HR, 1.5, (1.2-2.6) were independently correlated with OS. Conclusions: In elderly patients with stage III colon cancer lack of adjuvant chemotherapy, poor performance status, T4 or N2 high-risk disease, elevated baseline CEA, past history of a secondary cancer, elevated stage III colon cancer lack of adjuvant chemotherapy, poor performance status, T4 or N2 high-risk disease, elevated baseline CEA, past history of a secondary cancer, elevated NPNH ratio >0.1 and an ostomy formation correlate with inferior outcomes. Research Sponsor: University of Saskatchewan.

Use of novel cancer staging model to analyze healthcare costs of commercially insured patients with colorectal cancer. First Author: Rebecca Smith, Milliman, Inc., New York, NY

Background: Earlier colorectal cancer diagnosis can improve patient outcomes, but the payer cost impact of earlier staging is not clearly defined because stage identification is not directly available in administrative claims data. This gap impairs researchers' ability to fully evaluate the financial impact of earlier neoplasia detection resulting from colorectal cancer screening. In prior work, we used SEER-Medicare data to develop machine learning analytic models for estimating early-stage cancers (pts) (CC/E CRC) and at-risk pts vs at-risk RC at earlier disease onset and 1L therapy with real-world overall survival and time to next treatment (rwOS, rwTTNT) was estimated using Kaplan-Meier methods and hazard models adjusted for clinical confounders including year of metastatic diagnosis, group stage at initial diagnosis, site of disease, gender, race/ethnicity, and ECOG performance status. Results: Among 895 left-sided RAS/BRAF w/ CC pts, 216 and 679 pts had eo and mCRC, respectively. In pts treated with chemoradiotherapy vs. adjuvant chemotherapy, the adjusted hazard ratio (HR) (95% CI) of rwOS was 0.93 (0.56-1.53) and 0.77 (0.58-1.02) for eo and pts, respectively; the adjusted HR (95% CI) of mCRC was 0.96 (0.51-1.83) and 0.78 (0.57-1.07) in eo and pts, respectively. In pts treated with chemoradiotherapy vs. adjuvant chemotherapy, the adjusted HR (95% CI) of mCRC was 0.97 (0.58-1.63) and 0.73 (0.42-1.29) for eo and pts, respectively. Conclusions: Adding EGFRi to chemotherapy suggested potential improvements in rwOS and mCRC in eo pts but not in mCRC pts, similar to findings from prior literature. This data gap impairs researchers' ability to fully evaluate the financial impact of earlier neoplasia detection resulting from colorectal cancer screening. In prior work, we used SEER-Medicare data to develop machine learning analytic models for estimating early-stage cancers (pts) (CC/E CRC) and at-risk pts vs at-risk RC at earlier disease onset and 1L therapy with real-world overall survival and time to next treatment (rwOS, rwTTNT) was estimated using Kaplan-Meier methods and hazard models adjusted for clinical confounders including year of metastatic diagnosis, group stage at initial diagnosis, site of disease, gender, race/ethnicity, and ECOG performance status. Results: Among 895 left-sided RAS/BRAF w/ CC pts, 216 and 679 pts had eo and mCRC, respectively. In pts treated with chemoradiotherapy vs. adjuvant chemotherapy, the adjusted hazard ratio (HR) (95% CI) of rwOS was 0.93 (0.56-1.53) and 0.77 (0.58-1.02) for eo and pts, respectively; the adjusted HR (95% CI) of mCRC was 0.96 (0.51-1.83) and 0.78 (0.57-1.07) in eo and pts, respectively. In pts treated with chemoradiotherapy vs. adjuvant chemotherapy, the adjusted HR (95% CI) of mCRC was 0.97 (0.58-1.63) and 0.73 (0.42-1.29) for eo and pts, respectively. Conclusions: Adding EGFRi to chemotherapy suggested potential improvements in rwOS and mCRC in eo pts but not in mCRC pts, similar to findings from prior literature. This data gap impairs researchers' ability to fully evaluate the financial impact of earlier neoplasia detection resulting from colorectal cancer screening. In prior work, we used SEER-Medicare data to develop machine learning analytic models for estimating early-stage cancers (pts) (CC/E CRC) and at-risk pts vs at-risk RC at earlier disease onset and 1L therapy with real-world overall survival and time to next treatment (rwOS, rwTTNT) was estimated using Kaplan-Meier methods and hazard models adjusted for clinical confounders including year of metastatic diagnosis, group stage at initial diagnosis, site of disease, gender, race/ethnicity, and ECOG performance status. Results: Among 895 left-sided RAS/BRAF w/ CC pts, 216 and 679 pts had eo and mCRC, respectively. In pts treated with chemoradiotherapy vs. adjuvant chemotherapy, the adjusted hazard ratio (HR) (95% CI) of rwOS was 0.93 (0.56-1.53) and 0.77 (0.58-1.02) for eo and pts, respectively; the adjusted HR (95% CI) of mCRC was 0.96 (0.51-1.83) and 0.78 (0.57-1.07) in eo and pts, respectively. In pts treated with chemoradiotherapy vs. adjuvant chemotherapy, the adjusted HR (95% CI) of mCRC was 0.97 (0.58-1.63) and 0.73 (0.42-1.29) for eo and pts, respectively. Conclusions: Adding EGFRi to chemotherapy suggested potential improvements in rwOS and mCRC in eo pts but not in mCRC pts, similar to findings from prior literature.
Background: Colitis-associated cancer (CAC) is a devastating complication of inflammatory bowel disease. CAC tumor biology differs from that of sporadic colorectal cancer. EGFR inhibitor (EGFRi) w/ chemotherapy is standard of care for mCRC that is left (L) sided, RAS wild type (WT), without BRAF V600E mutation (mut) or ERBB2 amplification (amp). There are no published data on efficacy of EGFRi in CAC. We report outcomes of mCAC pts treated w/ EGFRi.

Methods: Cases were identified by querying a prospectively maintained database of CAC pts seen at Memorial Sloan K Sloan Cancer Center Cancer Institute, Singapore were discussed at a multidisciplinary tumor board. Patients Cancer Institute, Singapore were discussed at a multidisciplinary tumor board. Patients were eligible for TNT if they had cT2/3N+ or cT4Nany, threatened circumferential resection and 14.9% (n=7; 5 from PD, 1 from surgery-related complication, 1 unrelated to treatment) passed away. 1-year DFS rate was 88.7% (95% CI 75.0% - 95.2%).

Conclusions: Our findings show substantial variation in the choice of TNT sequence for locally advanced rectal cancer (LARC). This is the first Asian study reporting real-world data of TNT for LARC since its wide-scale adoption. pCR rates appear lower than reported studies. Under-reporting of outcomes in the published ARCAD nomogram as variables from the full model such as number and sites of metastases were unavailable in Flatiron. The C-index was used to validate the fitted models. The area under a time-dependent ROC (AUC) analysis was applied to indicate the predictive discrimination performance. Results: A total of 9710 pts, 5740 of whom were deceased were analyzed. The FRWC was older (54 ± 61) and had a poorer ECOG-PS (0.14 ± 0.6) compared to the ARCAD. A reduced ARCAD nomogram was derived from the full model (Table). The reduced nomogram calibration was as follows:

<table>
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Conclusions: Reduced ARCAD nomogram with multivariable cox model for 1-yr OS.

37 Poster Session

Total neoadjuvant therapy (TNT) for locally advanced rectal cancer (LARC): Real-world experience from a tertiary Asian cancer center.

First Author: Meng Wang, National University Cancer Institute, Singapore, Singapore

Background: Multiple studies of TNT for LARC have shown improved pathological complete response (pCR) rate and disease-free survival (DFS). However, real-world data in Asia is limited. We aimed to describe TNT practices in Asia, and to provide an international comparison with Memorial Sloan Kettering Cancer Center, Singapore were discussed at a multidisciplinary tumor board. Patients were eligible for TNT if they had cT2/3N+ or cT4Nany, threatened circumferential resection margin (CRM) and adequate organ function. TNT protocol was systemic chemotherapy with 5-6 cycles of mFOLFOX6 (5-fluorouracil, leucovorin, oxaliplatin) or 3-4 courses of XELOX (capecitabine, oxaliplatin) followed by short- or long-course chemomodulation (CRT), then 3 courses of mFOLFOX6 or 2 cycles of XELOX. Clinical outcomes and rates of complete response (cCR), pCR, surgery type, radiation DFS. Baseline pt demographics, laboratory results and tumor characteristics were analyzed to address these analyses. Results: 173/205 pts who were diagnosed with rectal cancer between February 2020 and November 2022 had LARC and 47 received TNT. Median age was 65 (range: 33-79), 68.1% male, 78.7% were Chinese, 19.2% had cT4 tumors, 87.2% node positive and 80.9% had CRM involvement. Median tumor distance from anal verge was 6cm (range: 1-115cm) on colonoscopy and 5cm (range: 2-12cm) on magnetic resonance imaging. 95.7% received XELOX, 87.0% had long-course CRT and 83.0% completed all cycles of systemic chemotherapy and CRT. 44.7% had dose reduction of systemic therapy and 4.3% required emergent surgery due to local complications during TNT. After TNT completion, 7 pts did not pursue surgery – 3 achieved cCR (6.4%) and adopted a watch-and-wait approach, 2 had disease progression (PD), and 2 declined. Of those who underwent surgery, 75% had splenectomy-preserving surgery and 10% achieved partial resection. 21.1% (n=1) achieved pCR. Rates of tumour regression grade (TRG) 0, 1, 2 were 7.5%, 15.0%, 67.5% and 10.0%, respectively. After a median follow-up of 21.7 months (range: 9.3 – 41.6 months), 21.3% (n = 10) had disease recurrence and 14.9% (n = 7) from PD, 1 from surgery-related complication, 1 unrelated to treatment) passed away. 1-year DFS rate was 88.7% (95% CI 75.0% – 95.2%).

Conclusions: These include immunohistochemistry for EGFR and its ligands, transcriptomic analyses to classify tumor molecular subtypes, and assessment of EGFR dependence and EGFR sensitivity in CAC organoids. Research Sponsor: None.

38 Poster Session

External validation of the ARCAD nomogram in a real-world cohort of patients with stage IV colorectal cancer (CRC).

First Author: James Yu, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: The ARCAD CRC nomogram is designed to predict 1-year survival in stage 4 CRC to assist with prognostication (JCO, JNCL, 2018). However, this nomogram was developed using patients (pts) enrolled in clinical trials. We sought to externally validate these data in a real-world cohort.

Methods: We used the Flatiron database from nationwide records collected from 2013-2020 to create a retrospectiveFlatiron real-world cohort (FRWC) of pts with historically confirmed stage 4 CRC. Pts with baseline blood tests prior to treatment (Tx) who had reached at least 1 line of Tx were included. Missing data (~5.5%) were imputed using R package missForest. A multivariable Cox regression model was fitted for overall survival (OS). The predictive performance of the published ARCAD nomogram as variables from the full model such as number and sites of metastases were unavailable in Flatiron. The C-index was used to validate the fitted models. The area under a time-dependent ROC (AUC) analysis was applied to indicate the predictive discrimination performance.

Results: A total of 9710 pts, 5740 of whom were deceased were analyzed. The FRWC was older (54 ± 61) and had a poorer ECOG-PS (0.14 ± 0.6) compared to the ARCAD. A reduced ARCAD nomogram was derived from the full model (Table). The reduced nomogram calibration was as follows:

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Conclusions: The ARCAD nomogram was validated in the very large FRWC. The observed underestimation of survival by the ARCAD nomogram in the FRWC is likely due to recent advances inTx options for CRC including targeted- or immunotherapy as the FRWC is more recent compared to pts in the original ARCAD cohort (1997-2002). Our findings indicate that the ARCAD nomogram is a promising decision-making tool for clinicians to predict 1 yr in real-world populations. Research Sponsor: None.

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Total neoadjuvant therapy for rectal cancer in the rural community oncology setting. First Author: Heidi Ann McKeen, Avera Cancer Institute Medical Oncology, Sioux Falls, SD

Background: The treatment of localized rectal adenocarcinomas with Total Neoadjuvant Therapy (TNT) has become the national standard. Data on the efficacy of TNT in a predominantly rural community oncology setting is limited. Methods: This ongoing retrospective analysis included 94 patients with proficient MMR Stage II or III rectal adenocarcinoma treated with traditional neoadjuvant treatment of chemoradiation followed by surgical resection +/- adjuvant chemotherapy, or Consolidation (chemotherapy upfront) TNT followed by surgical resection, diagnosed between 2017 and 2022 and treated at the Avera Cancer Institute in Sioux Falls, South Dakota. The primary objectives were to compare the pathologic response and treatment completion rates in patients with rectal cancer treated with TNT with patients treated with traditional neoadjuvant treatment. The secondary objective was to compare the pathologic response rate for TNT at different tumor locations. Results: Of 94 patients assessed, 54 patients received traditional neoadjuvant therapy and 40 patients received TNT. For patients treated with traditional neoadjuvant therapy, 43% (n=23) completed all recommended treatment, with 63% (n=34) achieving a partial response (PR) and 19% (n=10) a complete pathologic response (CR). For patients treated with TNT, 93% (n=37) completed all recommended treatment, and 68% (n=27) achieved a PR and 15% (n=6) achieved a CR. For patients that received Consolidation TNT (n=21), 66% (n=12) achieved a PR and 21% (n=4) achieved a CR. For patients that received induction TNT (n=19), 68% (n=13) achieved a PR and 11% (n=2) achieved a CR. For patients with high tumor location (n=4) treated with TNT, 50% (n=2) achieved a PR and 25% (n=1) achieved a CR. For patients with mid tumor location (n=18) treated with TNT, 67% (n=12) achieved a PR and 22% (n=4) achieved a CR. For patients with low tumor location (n=18) treated with TNT, 72% (n=13) achieved a PR and one patient (6%) achieved a CR. Conclusions: The treatment of rectal adenocarcinoma with TNT in a predominantly rural community oncology setting is achievable with a higher completion rate compared to traditional neoadjuvant treatment. Our results also show a trend toward a higher complete pathologic response rate in Consolidation compared to Induction approach and in high/mid rectal tumors compared to low rectal tumors. Future work will be conducted to assess any differences in recurrence and survival. Research Sponsor: None.

The efficacy of chemotherapy for colorectal cancer with early recurrence after adjuvant chemotherapy. First Author: Dai Okemoto, Osaka Medical and Pharmaceutical University, Takatsukasi, Osaka, Japan

Background: Adjuvant chemotherapy is the standard treatment for patients with stage III colorectal cancer (CRC) underwent surgery. However, the efficacy of chemotherapy for early recurrence after adjuvant chemotherapy remains unclear. This study aimed to assess the efficacy of chemotherapy for CRC with early recurrence during or after adjuvant chemotherapy. Methods: We retrospectively reviewed CRC patients who underwent surgery at 3 institutions between 2016 and 2021. The inclusion criteria were as follows: EGFR performance status was 0 or 1, histology was adenocarcinoma, patients who received adjuvant chemotherapy following surgical resection, early recurrence during or within 12 months after adjuvant chemotherapy and no prior treatment for CRC after early recurrence. The interval from the last administration of adjuvant chemotherapy to recurrence was defined as the recurrence-free interval (RFI). Overall survival (OS), progression-free survival (PFS), objective response rates (ORR), and disease control rate (DCR) were assessed according to the RFI. Results: Of 448 patients, 32 patients were eligible. Median age was 57 years (range 26-79), 14 patients (44%) were male and ECOC performance status 0 / 1 was 29 (91%) / 3 (9%). LAS wild-type / mutant was 12 (38%) / 20 (62%) and left / right as seesiness was 21 (66%) / 11 (34%). Regarding adjuvant chemotherapy, 4 patients (12%) received single-agent therapy, while 28 patients (86%) received combination therapy with two agents. Palivitamotherapy after early recurrence included Oxaliplatin-based regimens in 13 patients (41%), irinotecan-based regimens in another 13 patients (41%), and other regimens in 6 patients (18%). For all patients, the median PFS and OS were 10.4 months and 43.0 months, respectively. The ORR and DCR were 34.4% and 75.0%, respectively. When patients were divided into RFI < 6 months and RFI ≥ 6 months, the ORR was superior in the RFI ≥ 6 months group to RFI < 6 months group (56% vs. 26%). The PFS (median 10.4 months vs. 17.8 months, HR 0.92, 95% CI 0.36-2.38, p = 0.87) and OS (median 31.3 months vs. 43.0 months, HR 0.96, 95% CI 0.31-3.08, p = 0.97) did not differ between the RFI < 6 months group and the RFI ≥ 6 months group. Multivariate analysis for OS and PFS showed a trend in favor of CRC in the RFI ≥ 6 months group compared to the RFI ≤ 6 months group (HR 1.95, 95% CI 0.35-9.8, p = 0.48). Conclusions: In patients with CRC experienced early recurrence, the RFI < 6 months group had a trend of poor efficacy compared to the RFI ≥ 6 months group. Research Sponsor: None.

COLORECTAL CANCER

Assessing risk stratification in long-term outcomes of rectal neuroendocrine tumors following endoscopic resection: A multicenter retrospective study. First Author: Yeonjoo Seo, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Background: The detection of rectal neuroendocrine tumors (NETs) has increased with advances in diagnostic endoscopy. Endoscopic resection (ER) is a highly effective treatment option for rectal NETs confined to. We aimed to analyze the long-term outcomes of patients with rectal NETs after ER. Methods: In this multicenter retrospective study, we included patients who underwent ER of rectal NETs from 2009 to 2018 and were followed for ≥12 months at five university hospitals. We classified the patients into three risk groups according to the clinicopathological status of the rectal NET: low, indeterminate, and high. The high-risk group was defined if the tumors have any of the following: size ≥ 10 mm, lymphovascular invasion, muscularis propria or deeper invasion, positive resection margins, or mitotic count ≥2/10. Results: In total, 346 patients were included, with 144 (41.6%), 121 (35.0%), and 81 (23.4%) patients in the low, indeterminate, and high risk groups, respectively. In the high-risk group, seven patients (7/81, 8.6%) suffered salvage treatment 28 (27-67) days after the initial ER. There was no extracolonic recurrence in any of the 7 patients. During the follow-up period, 59% of all included patients, 1.1% (4/346) had extracolonic recurrences at 56.6 (34.7-73.0) months after initial ER. Three of these patients (7%) were at a high risk without salvage treatment. The risk of extracolonic recurrence was significantly higher in the high-risk group than in the other groups (p=0.039). Conclusions: The risk of extracolonic recurrence following ER is low. However, patients with high-risk tumors should be monitored for the possibility of metastasis during long-term follow-up of high-risk patients and consider salvage treatment. Research Sponsor: Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science and ICT (NRF-2018M3A9B6021507).

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Real-world (RW) testing patterns of serum lactate dehydrogenase (LDH) and its prognostic value among patients (pts) with metastatic colorectal cancer (mCRC). First Author: Richard D. Kim, Moffitt Cancer Center, Tampa, FL

Background: Anecdotal evidence suggests that some pts with mCRC experience significantly longer overall survival (OS) when receiving chemotherapy (CT) for mCRC in the USA. Prognostic/clinical characteristics of pts with long-term response (LTR) to REG are lacking. We evaluated demographic/clinical characteristics of pts with long-term response (LTR) of REG to CT for mCRC using the US nationwide de-identified Flatiron Health Electronic Health Record-derived database. The study period was January 1, 2013 to May 31, 2023, and adult pts with mCRC who initiated REG monotherapy from January 1, 2019 to April 30, 2022, were included. LTR of REG was defined as 3 months of continuous REG therapy with no subsequent therapy for a minimum of 5 months. We evaluated demographic/clinical characteristics of pts with LTR5 (primary objective; after 5 months) and LTR4 (secondary objective) compared with 1L and 2L REG treatment cycles.

Methods: This was a retrospective cohort study using the US nationwide de-identified Flatiron Health Electronic Health Record-derived database. The study period was January 1, 2013 to May 31, 2023, and adult pts with mCRC who initiated REG monotherapy from January 1, 2019 to April 30, 2022, were included. LTR of REG was defined as 3 months of continuous REG therapy with no subsequent therapy for a minimum of 5 months. We evaluated demographic/clinical characteristics of pts with LTR5 (primary objective; after 5 months) and LTR4 (secondary objective) compared with 1L and 2L REG treatment cycles.

Results: Overall, 355 pts (France, n=146; Italy, n=141; Belgium, n=68; male, 54% aged ≥65 years) were eligible for inclusion. Nearly half (49%) received a REG-like regimen; 32% received a standard regimen, and 19% received a dose-adjusted regimen (Table). A higher proportion of pts on a dose-adjusted regimen had ≥3 metastatic sites (64% vs 43% for standard dosing) and most had initiated ≥3 REG cycles (93% vs 67% and 64% for REG-like and standard dosing, respectively). Pts receiving a REG-like dosing regimen had a worse performance status (ECOG PS ≥2; 35% vs 30% for dose-adjusted and standard dosing) and a higher proportion of KRAS (42% vs 37% and 30% for dose-adjusted and standard dosing regimens, respectively) or NRAS (28% vs 24% and 21% for dose-adjusted and standard dosing regimens, respectively) mutations. Median DoT was longer for REG-like and dose-adjusted regimens vs standard dosing (1.4 and 1.9 vs 1.0 months, respectively; Table). Conclusions: Pts receiving dose-adjustable dosing regimens (REG-like, dose-adjusted) had longer REG DoT compared with a standard dosing regimen despite having a higher frequency of adverse prognostic factors. Thus, this study affirms that flexible dosing strategies are viable options for optimizing REG treatment outcomes and pts with mCRC. Research Sponsor: Bayer.

Poster Session

Real-world (RW) testing in patients (pts) with metastatic colorectal cancer (mCRC) with long-term responses to regorafenib in the USA. First Author: Richard D. Kim, Moffitt Cancer Center, Tampa, FL

Background: Anecdotal evidence suggests that some pts with mCRC experience significantly longer overall survival (OS) when receiving chemotherapy (CT) for mCRC in the USA. Prognostic/clinical characteristics of pts with long-term response (LTR) to REG are lacking. We evaluated demographic/clinical characteristics of pts with long-term response (LTR) of REG to CT for mCRC using the US nationwide de-identified Flatiron Health Electronic Health Record-derived database. The study period was January 1, 2013 to May 31, 2023, and adult pts with mCRC who initiated REG monotherapy from January 1, 2019 to April 30, 2022, were included. LTR of REG was defined as 3 months of continuous REG therapy with no subsequent therapy for a minimum of 5 months. We evaluated demographic/clinical characteristics of pts with LTR5 (primary objective; after 5 months) and LTR4 (secondary objective) compared with 1L and 2L REG treatment cycles.

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Poster Session

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Background: Anecdotal evidence suggests that some pts with mCRC experience significantly longer overall survival (OS) when receiving chemotherapy (CT) for mCRC in the USA. Prognostic/clinical characteristics of pts with long-term response (LTR) to REG are lacking. We evaluated demographic/clinical characteristics of pts with LTR5 (primary objective; after 5 months) and LTR4 (secondary objective) compared with 1L and 2L REG treatment cycles.

Methods: This was a retrospective cohort study using the US nationwide de-identified Flatiron Health Electronic Health Record-derived database. The study period was January 1, 2013 to May 31, 2023, and adult pts with mCRC who initiated REG monotherapy from January 1, 2019 to April 30, 2022, were included. LTR of REG was defined as 3 months of continuous REG therapy with no subsequent therapy for a minimum of 5 months. We evaluated demographic/clinical characteristics of pts with LTR5 (primary objective; after 5 months) and LTR4 (secondary objective) compared with 1L and 2L REG treatment cycles.

Results: Overall, 355 pts (France, n=146; Italy, n=141; Belgium, n=68; male, 54% aged ≥65 years) were eligible for inclusion. Nearly half (49%) received a REG-like regimen; 32% received a standard regimen, and 19% received a dose-adjusted regimen (Table). A higher proportion of pts on a dose-adjusted regimen had ≥3 metastatic sites (64% vs 43% for standard dosing) and most had initiated ≥3 REG cycles (93% vs 67% and 64% for REG-like and standard dosing, respectively). Pts receiving a REG-like dosing regimen had a worse performance status (ECOG PS ≥2; 35% vs 30% for dose-adjusted and standard dosing) and a higher proportion of KRAS (42% vs 37% and 30% for dose-adjusted and standard dosing regimens, respectively) or NRAS (28% vs 24% and 21% for dose-adjusted and standard dosing regimens, respectively) mutations. Median DoT was longer for REG-like and dose-adjusted regimens vs standard dosing (1.4 and 1.9 vs 1.0 months, respectively; Table). Conclusions: Pts receiving dose-adjustable dosing regimens (REG-like, dose-adjusted) had longer REG DoT compared with a standard dosing regimen despite having a higher frequency of adverse prognostic factors. Thus, this study affirms that flexible dosing strategies are viable options for optimizing REG treatment outcomes and pts with mCRC. Research Sponsor: Bayer.

Poster Session

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Recurrence in the pelvic side wall after lateral lymph node dissection for rectal cancer. First Author: Misato Takao, Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

**Background:** Locally advanced rectal cancer poses a persistent challenge due to the risk of local recurrence, which impacts patient outcomes and quality of life. To address this, lateral pelvic lymph node dissection (LPND) has emerged as a surgical approach to improve local control. However, comprehensive studies evaluating the outcomes and patterns of recurrence after LPND are limited. This retrospective study aimed to fill this gap and provide insights into the effectiveness of LPND. **Methods:** We conducted a retrospective analysis of 515 patients diagnosed with stage III lower rectal cancer who underwent TME and LPND between January 2005 and August 2022. Clinicopathological data were collected, and tumor staging followed the TNM classification system. Recurrence patterns, survival rates, and factors influencing lateral pelvic recurrence were assessed. **Results:** In our cohort, 18.8% of patients had pathologically positive lateral lymph nodes. Patients with lateral lymph node metastasis exhibited significantly lower 5-year relapse-free survival (31.6%) and overall survival (47.8%) rates compared to those without metastasis (69.5% and 84.7%, respectively). Local recurrence occurred in 20.1% of all patients, with 6.7% experiencing lateral pelvic recurrence (LPR) and 17.4% central pelvic recurrence. Multivariate analysis identified age over 75, lateral lymph node metastasis, and adjuvant chemotherapy as independent risk factors for LPR.

**Conclusions:** Lateral pelvic lymph node dissection remains a valuable tool in managing locally advanced rectal cancer. Our findings underscore the importance of surgeon expertise in performing LPND and the potential benefits of combining treatments to further reduce lateral recurrence. LPND should continue to be explored and refined to increase its efficacy in performing LPND and the potential benefits of combining treatments to

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Real-world effectiveness and safety of trifluridine-tipiracil (FTD/TPI) and bevacizumab (BEV) in refractory metastatic colorectal cancer (mCRC): The BeTAS trial. First Author: Nieves Martinez Lago, Complejo Hospitalario Universitario de Ferrol, Ferrol, Spain

**Background:** In the Sunlight Trial, the combination of FTD/TPI + BEV demonstrated significantly extended Overall Survival (OS) and Progression-Free Survival (PFS), along with an improved Disease Control Rate (DCR), compared to FTD/TPI alone in patients with refractory mCRC. The BeTAS trial aimed to evaluate the real-world effectiveness and safety of the FTD/TPI + BEV combination in patients with refractory mCRC. **Methods:** We conducted a multicenter, retrospective, observational study involving patients with mCRC who were refractory or intolerant to standard therapies (including oxaliplatin, irinotecan, fluoropyrimidines, anti-VEGF, and anti-EGFR) as per local guidelines. Patients were treated with FTD/TPI + BEV at six university hospitals affiliated with the Galician Research Group on Digestive Tumors (GiTUD) in Northwest Spain. **Results:** A total of 110 patients were enrolled in the BeTAS trial between July 2019 and August 2023. The median age was 66 years (range 33-88 years), with 62.7% being male. Notably, 18.2% of patients had an ECOG performance status of 2, 50.9% had RAS mutations, 18.8% of patients had pathologically positive lateral metastases, and 72.7% had liver metastases. Additionally, 26.4% had a history of tobacco use, 18.8% of patients had an ECOG performance status of 2, 50.9% had RAS mutations, 18.8% of patients had pathologically positive lateral metastases, and 72.7% had liver metastases. Additionally, 26.4% had a history of tobacco use, and 18.2% of patients had an ECOG performance status of 2.

**Conclusions:** The BeTAS trial findings affirm the real-world effectiveness and safety of FTD/TPI + BEV in the context of routine clinical practice, even in a population with a poor prognosis and extensive prior treatment history. Research Sponsor: None.

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The efficacy of adjuvant chemotherapy after total mesorectal excision with selective lateral pelvic node dissection for lower rectal cancer. First Author: Katsuyuki Kameshi, Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University, Takatsuki, Japan

**Background:** The standard strategy for lower rectal cancer (LRC) is Neo-adjuvant chemoradiotherapy (CRT) plus total mesorectal excision (TME) in Western countries. TME with or without lateral pelvic node dissection (LND) followed by adjuvant chemotherapy is the standard treatment for LRC in Japan. However, the efficacy of adjuvant chemotherapy for LRC after TME without LND remains unclear. The aim of this study was to assess the efficacy of adjuvant chemoradiotherapy for LRC after TME without LND. **Methods:** We retrospectively reviewed patients who underwent R0 resection by TME without LND and received adjuvant chemotherapy between 2010 and 2020 at our institution. The inclusion criteria were as follows: age ≥ 20 years; histologically confirmed adenocarcinoma; pathological stage III (UICC B); lower rectal cancer (Ra/Rb); patients who received adjuvant chemotherapy after R0 resection without LND and no prior treatment before surgery. We evaluated relapse free survival (RFS) and overall survival (OS) in patients with LRC. Prognostic impact of location, adjuvant chemotherapy regimens, T factor, and N factor on RFS was explored by a multivariate analysis. **Results:** From a total of 197 patients, 117 patients were eligible. Median age was 65 years (range 26-82) and 54 patients (46%) were male. Tumor location was 67% (57/85) (43%) for Ra/Rb and pathologic stage was 47% (40/85) (61%) (95% CI: 0.6-0.9). The 5-year RFS rates and 5-year OS rates were 33% (95% CI: 18.5-47.2) and 65% (95% CI: 47.7-82.4), respectively. The 3-year RFS rates and 3-year OS rates were 70% (95% CI: 59.0-81.1) and 95% (95% CI: 89.9-98.1). The 5-year RFS rates according to tumor location (Ra/Rb) and adjuvant chemotherapy regimens (single agent/doublet) were 76.9%/70.7% and 71.8%/68.5%, respectively. The 3-year RFS rates based on pathological stage (I/II/IIIC) were 76.7%/68.4%/64.8%. In a multivariate analysis, T3/4 were identified as an independent poor prognostic factor for RFS (p = 0.06). Conclusions: TME without LND demonstrated favorable 3-year RFS rate, adjuvant chemotherapy regimens after TME without LND suggested no additive efficacy of oxaliplatin on RFS. Research Sponsor: None.
53 Poster Session

Real-world treatment patterns and unmet need in patients with previously treated metastatic colorectal cancer that is not MSI-H or dMMR. First Author: Katherine Desai, Merck & Co., Inc., Rahway, NJ

Background: Regorafenib and trifluridine/tipiracil (TAS-102) are standard of care (SoC) systemic anticancer treatments (SACT) for metastatic colorectal cancer (mCRC) patients previously treated with fluoropyrimidine (5-FU), irinotecan, & oxaliplatin-based chemotherapy. However, evidence is limited on post-chemotherapy & later SACT for patients with mCRC that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) this study assessed real-world mCRC treatment patterns and treatment patterns in community oncology practices among previously treated, not MSI-H/dMMR mCRC patients. Methods: This retrospective cohort study utilized The US Oncology Network (iKnowMed) electronic health record database, supplemented by chart review. The study cohort comprised adult, not MSI-H/dMMR mCRC patients treated with chemotherapy (5-FU/capcitabine, irinotecan, and oxaliplatin) who initiated subsequent SACT or received best supportive care (BSC) between 1/1/2016 & 12/31/2021. Index date for SACT users was the regimen start date. For patients on BSC and no subsequent SACT/BSC, index date was last chemotherapy administration date. Patients were followed from index date through 6/31/2022, date of death or last contact date, whichever occurred first. Descriptive statistics were used to report patient and treatment characteristics. Results: The study consisted of 292 mCRC patients, with a median age of 57 (range: 49-68) years. The predominant histology was adenocarcinoma (n = 237, 83.1%) with 1.7% other histology and 1.2% unknown. The most predominant comorbidities were cardiovascular disease (n = 149, 50.8%) and diabetes mellitus (n = 120, 40.9%). Eighty-seven (29.8%) patients received at least one chemotherapy and 67 (22.8%) patients received immunotherapy in subsequent lines. This highlights an unmet need in this population.

54 Poster Session

Patient-reported outcomes from the BESPOKE CRC study. First Author: Padshoorn Murtaza Kasi, Weill Cornell Medicine, Englewood Institute on Precision Medicine, NewYork-Presbyterian Hospital, New York, NY

Background: BESPOKE CRC is a multicenter, prospective, observational study that investigates the clinical utility of ctDNA for optimal use of adjuvant chemotherapy and early detection of recurrence in patients with CRC surgery with complex resection. The perceived utility and impact of ctDNA testing results has on pts’ anxiety about cancer recurrence is not entirely known. Herein, we formally report perceived utility and dimensions of well being among CRC patients cared for at an academic medical center.

Methods: In this prospective, single-arm, longitudinal study, we enrolled 170 pts with stages II–IV CRC were enrolled and followed for a median of 16.6 months with serial ctDNA analysis using a personalized, tumor-informed assay (SignateraTM, Naner, Inc.). An optional survey was collected at the time of enrollment and at 4 and 12 weeks (w), 6, 12, 18 and 24 months after surgery. The survey was administered by East Hanover, NJ Hospital Research & Clinical Studies (HARDS), (2) Fear of Cancer Recurrence (FCR-4), (3) National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Colorectal Symptom Index-19 items (NCCN-FACT FCSI-19 version 2), and (4) ctDNA utility questionnaire (perceived utility and impact of ctDNA test results on pts’ anxiety about recurrence). The score ranges were: HADS: 0 (no) to 21 (valid) anxiety/depression; FCR-4: 0 (minimal) to 20 (maximum) fear of cancer recurrence; FCSI-19: 0 (severely symptomatic) to 76 (asymptomatic); ctDNA utility: 5 strongly agree, 4 agree, 3 neutral, 2 disagree, 1 strongly disagree. Results: A total of 1129/1123/1125/1136 responses from 414/413/413/418 pts were received for HADS/FCR-4/FCSI-19/ctDNA questionnaires, respectively. When compared between ctDNA-negative and -positive pts, FCR-4 and FCSI-19 surveys revealed numerical differences in pts’ mean FCR-4/FCSI-19 scores, although statistically significant (FCR-4: 9.1 vs 10.4, p < 0.01; FCSI-19: 58.6 vs. 53.8, p = 0.001). No significant differences in the anxiety and depression scores (HADS) were found between ctDNA-negative and -positive pts. Further analysis of the responders who reported the received information from received ctDNA results, and 86% said they would continue using the ctDNA test to monitor cancer. Regardless of the ctDNA results, 74% of pts reported feeling they were receiving the right treatment after receiving their results. ctDNA results reduced anxiety about cancer recurrence in 62% of pts. Notably, ctDNA-negative pts felt less anxious of recurrent compared to ctDNA-positive pts (average score 4.01 vs 3.57, p = 0.001). Conclusions: Most responders valued the information they received through the personalized, tumor-informed ctDNA tests and would continue ctDNA testing. Pts with ctDNA positive results felt slightly more anxious about CRC recurrence, while ctDNA-negative pts reported reduced anxiety levels. Our results for the first time show the important dimensions of pt well being and perceived utility of ctDNA testing in pts with CRC. Clinical trial information: NCT04246702. Research Sponsor: None.
Reproductive and fertility-related challenges in female patients diagnosed with early-onset colorectal cancer. First Author: Rachel M. Seifert, University of Utah, Salt Lake City, UT.

Background: Incidence of early-onset colorectal cancer (EOCRC, defined as onset < 50 years) is on the rise, with rates increasing by 51% from 2000-2015. Knowledge of fertility concerns in patients with EOCRC is important to provide the resources needed for this group. The aim of this study is to examine reproductive concerns after cancer diagnosis in female COLONTOWN patients with EOCRC using a validated and standardized questionnaire “Reproductive Concerns After Cancer” (RCAC). Methods: Female survivors (N=89, age at diagnosis 20 to 47 years) with EOCRC diagnosis were recruited from COLONTOWN. In order to capture the impact of EOCRC diagnosis on sexual health and fertility, a 51-question survey was created that included the RCAC scale as well as questions about pregnancy history, whether fertility preservation counselling occurred, self-reported demographics, and tumor and treatment. RCAC includes 6 subdomains on fertility preservation, partner disclosure on fertility status, child health, personal health, acceptance of possible infertility, and becoming pregnant, with total score being the sum of these domains. Data collected was analyzed using means, ranges, and standard deviations for continuous variables and frequencies and chi squared tests for categorical variables. Results: The mean age at diagnosis was 35 ± 5 years. 72% had discussions with a medical professional about fertility preservation after receiving their cancer diagnosis. Patients with rectal cancer were more likely to have this discussion compared to patients with colon cancer (p=0.04); tumor stage did not affect likelihood of having a fertility discussion (p>0.05). Seventeen (19%) underwent subsequent fertility preservation. Patients with stage IV cancer were less likely to undergo fertility preservation compared to those with stage III cancer (p=0.02), the decision to undergo fertility preservation was not affected by tumor site (p>0.05). 13% of all patients had insurance that would cover fertility preservation. Notably, 33% (37/112) of patients said they would have considered fertility preservation if it were covered by insurance, and this was not impacted by tumor site or stage (p>0.05). RCAC subscale scores were 3.47 for fertility preservation, 2.50 for partner disclosure of fertility status, 4.09 for child’s health, 3.88 for personal health, 2.27 for acceptance of possible infertility, and 3.49 for becoming pregnant. Conclusions: This study provides evidence that some patients with EOCRC experience concerns about fertility. Patients endorsed concern for child’s health and personal health over fertility preservation. Notably, 37% would have considered fertility preservation had it been covered by insurance. This study provides characterization of the fertility-related concerns of EOCRC survivors and supports the future development of resources and policies to support these patients. Research Sponsor: Utah Grand Challenges Grant.

Survival benefit and clinical characteristics of patients with metastatic colorectal cancer (mCRC) receiving pulmonary metastasectomy. First Author: Javier Soto Alsar, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain.

Background: The role of lung metastasectomy in mCRC remains a topic of particular interest. Recent studies have shown that patients with localized pulmonary metastases have better survival outcomes. Our aim was to identify clinical and molecular differences and survival data of patients who received lung metastasectomy versus patients who did not. Results: Among all patients, 36 (31.3%) received pulmonary metastasectomy. Patients undergoing metastasectomy resection had more frequently ECOG 0 (51.4% vs 20.8%, p = 0.001), resected primary tumor (100% vs 78.5%, p = 0.0026), metastatic disease (75% vs 46.8%, p = 0.0048) and a single metastatic location (79.4% vs 41%, p = 0.0002). In addition, none of them had BRAF mutation (0% vs 17.1%, p = 0.04); however, no statistically significant differences were found regarding KRAS, NRAS, PIK3CA, HER2 or presence of microsatellite instability (MSI). Patients who received lung metastasectomy had higher BMI (26.1 ± 4.4 vs 23.3, p = 0.037) and lower median levels of CEA (19.5 ± 142.9 vs 0.007), CA 19.9 (30.6 ± 244.9, p = 0.011) and LDH (159 ± 211.9, p = 0.018). We found an OS benefit in patients undergoing metastasectomy (median not reached (NR) vs 41.4 months, HR for death 0.27, 95% CI 0.14 - 0.53, p = 0.000); a multivariate analysis confirmed that this benefit was independent from the characteristics mentioned above. The median progression-free survival (PFS) after metastasectomy resection was 53.3 months. Conclusions: In our study, patients who were more likely to receive lung metastasectomy were those with ECOG 0, resected primary tumor, metastasectomy disseminated disease, a single metastatic location, native BRAF mutation status and low CEA, CA 19.9 and LDH levels, with a significant OS benefit associated. Research Sponsor: None.

Clinical characteristics and survival analysis in patients with isolated pulmonary metastases from colorectal cancer (CRC). First Author: Javier Soto Alsar, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain.

Background: Recent studies seem to indicate that patients with metastatic colorectal cancer (mCRC) with exclusive pulmonary metastatic disease have better outcomes than those with other metastatic sites. The aim of this study is to identify differences in clinical and survival characteristics between the two groups in a cohort of a third level hospital. Methods: We retrospectively analyzed a sample of 569 patients with mCRC in a tumor registry from 2015 to 2021, analyzing clinical and molecular characteristics, as well as overall survival data of patients with isolated metastases. Results: Of the total sample analyzed, 61 patients (10.7%) had isolated pulmonary metastases. In these patients, several clinical characteristics were more frequent: primary rectal tumor (52.5% vs 23.4%, p < 0.000), resected primary tumor (95.1% vs 78.9%, p = 0.0026), metastatic disease (62.3% vs 42%, p = 0.0025) and complete response rate to the first line of treatment (19.3% vs 9.9%, p = 0.026). Furthermore, analytically, these patients were more likely to have normal CEA (75% vs 38.3%, p < 0.000), CA 19.9 (84.3% vs 57.7%, p = 0.0002) and LDH (91.6% vs 66.5%, p = 0.0007) levels. In our cohort, we found no statistically significant differences in tumor mutational status (KRAS, NRAS, BRAF, PIK3CA and HER2). There were no patients with exclusive metastatic disease and microsatellite instability (MSI). 70.5% of patients with isolated pulmonary metastases received lung metastasectomy, and up to 58.3% received a second metastasectomy. We also found a numerical benefit in terms of overall survival (OS) in patients with exclusive metastatic lung disease, although it did not reach statistical significance (median OS 77.3 vs 58.1 months, HR for death 0.7, 95% CI 0.49 – 1.01, p = 0.083). Conclusions: In our cohort, patients with isolated pulmonary metastases were more likely to have rectal tumors, primary tumor resection, metastasectomy resection, higher rate of complete responses and normal CEA, CA 19.9 and LDH levels, with a possible benefit in terms of OS. Research Sponsor: None.
Background: Colorectal cancer (CRC) is one of the most commonly diagnosed cancer both in Mexico and worldwide, with the peak incidence in patients ≥65 years. The use of adjuvant chemotherapy (CT) improves the prognosis of high-risk CRC. The benefit from fluorouracil (FU)-based CT across all age groups is not questionable, but the use of oxaliplatin (Ox) is controversial. Methods: Original, retrospective, observational study. Included patients diagnosed with CRC adenocarcinoma treated at the Instituto Nacional de Cancerología Mexico, between 2004 to 2022. Statistical analysis required: X² and t-test, Kaplan Meier, Log Rank, and Cox Regression. Statistical significance differences were assessed when p was bilaterally <0.05. Results: From 1,238 patients with localized CRC, 275 patients were included in analysis and divided into 2 groups: young (≤30 years) (n = 54) and older (≥70 years) (n = 221). Most patients were male for both groups (55%). Comorbidities were observed in 2% of young patients and 51% of older patients (p < 0.001). Stages were: I (31%), II (33%), III (49%), and IV (7%). CT was received in 70% of young and 47% of older patients (p = 0.002). Regarding CT regimens, 56% and 21% of young and older patients respectively, had oxaliplatin (p < 0.001), while 21% of young and 32% of older patients did not complete the CT (p = 0.012). Overall survival (OS) analysis was performed considering age and S-II median-OS was not reached (NR) for both groups, while S-III median-OS was 170 months (m) for young versus NR for older (p = 0.690). When including CT in OS analysis, patients S-II median-OS was NR for all groups (p = 0.081), while S-III median-OS was 170 m with 19 m without CT for young versus NR with and 99 m without CT for older, respectively (p = 0.010; 95% CI: 0.59-0.72); Cox Regression analysis showed significant association between CT and survival (HR 0.71; 95% CI: 0.52-0.95; p = 0.025) with 76% versus 60% patients treated with and without Ox respectively (p = 0.030, 95% CI 0.25-0.93). In Cox-Regression analysis for patients with clinical stage III, regimen completion (p = 0.004; HR 0.38, 95% CI 0.01-0.78) and Ox (p = 0.022; HR 0.43, 95% CI 0.13-0.83) were significant predictors for OS. Conclusion: There was no evidence which compare the admission of CT between young and older patients or the description of these populations in Mexico. Young patients are more likely to receive CT with Ox presumably due to the lack of comorbidities and life expectancy. The benefit of CT on OS in young patients is not in question. An increase in OS was found in older patients who received CT with Ox, but a higher percentage of treatment discontinuation was observed secondary to toxicity. As recommended by the literature, its essential to integrate assessment in older patients to determine which patients will benefit from complete CT regimens to increase their OS, apart from their chronological age. Research Sponsor: None.

Real-world comparison of low- versus high-dose continuous SFU infusion in patients receiving triplet chemotherapy plus bevacizumab for newly diagnosed metastatic colorectal cancer (mCRC). First Author: William Joseph Chapin, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA

Background: Several randomized trials demonstrated an overall survival (OS) benefit to triplet chemotherapy (5-FU, oxaliplatin, and irinotecan) plus bevacizumab compared to doublet chemotherapy plus bevacizumab in patients with newly diagnosed mCRC, though with higher rates of neutropenic fever and diarrhea. These trials used high-dose continuous infusion 5-FU (2,200 mg/m²/48 hours), but national guidelines suggest low-dose continuous infusion 5-FU (750-800 mg/m²/48 hours) due to lower tolerance in US patients. We performed a retrospective cohort study in a U.S. population to compare the effectiveness of low- vs high-dose continuous infusion SFU in patients undergoing triplet chemotherapy plus bevacizumab for newly diagnosed mCRC. Methods: We used the Flatiron Health electronic health record-derived database, comprising de-identified patient-level structured electronic health records from ~280 cancer clinics. Patients with newly diagnosed mCRC who initiated triplet chemotherapy plus bevacizumab between 10/23/14 and 10/31/22 with non-missing height, weight, and dosing data were included. SFU infusion doses of 2,000 – 2,799 mg/m² were categorized as low-dose while those ≤2,800 mg/m² were categorized as high-dose. OS from first-line treatment initiation was assessed by dosing group using the Kaplan Meier method with log-rank testing. Multivariable analysis with adjustment for pre-specified variables with imbalance (defined by standardized difference < 0.10) was performed using multivariable Cox proportional hazards modeling. Missing data were imputed using multiple imputation with chained equations. Results: Among 520 patients included, 244 received low-dose and 76 patients received high-dose continuous infusion SFU. Imbalance between low- and high-dose groups was observed in the use of SFU bolus (23% vs 3%), year of metastatic diagnosis 2018-2022 (80% vs 55%), mean irinotecan dose (156.4 vs 160.5 mg/m²), left-sided primary (73% vs 64%), and female (54% vs 65%) and metastases at diagnosis (HR 0.75 vs 1.42). OS in patients receiving triplet chemotherapy plus bevacizumab, there was no association with survival between low- vs high-dose continuous infusion SFU. This supports current guidelines recommending low-dose continuous infusion SFU (2,400mg/m²/48 hours) for patients with mCRC receiving triplet chemotherapy in the U.S. Research Sponsor: None.

Retrospective analysis of the real-world demographics, clinical characteristics, and treatment patterns in metastatic CRC among patients treated with encorafenib in combination with cetuximab in the United States. First Author: Aparna Raj Parikh, Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: The BRAF V600E mutation (BRAF-m) occurs in approximately 7% of patients with metastatic CRC (mCRC). Encorafenib (enco) in combination with cetuximab (cetux) was approved in April 2020 as the first targeted regimen for the treatment of adult patients with BRAF-m mCRC. The purpose of this study is to assess the demographics, clinical characteristics, and treatment patterns in BRAF-m mCRC among patients treated with enco, based on a claims database in the US. Methods: This was a retrospective cohort study in the IQVIA PharMetrics Plus claims database. Adults ≥18 years old with ≥1 claim for enco (first claim for enco on/after 4/1/2020) with concurrent cetux, as approved, or with EGFR panitumumab (pani), ≥2 ICD-9/10 codes for malignancy of the colon or rectum ≥30 days apart in the 1 year before index date, and ≥1 day of pharmacy and medical continuous enrollment during the index date were included. Patients were excluded if they had a record of melanoma or non-small cell lung cancer during the year before index date, were enrolled in a clinical trial any time after the CRC diagnosis date or did not have a treatment regimen starting on or after CRC diagnosis date. Index date was the date of first treatment of enco+EGFR during the identification period (4/1/2020-3/1/2022). Patient demographics and disease characteristics were assessed at baseline, and treatment patterns were evaluated during the pre-index and follow-up periods. Results: 125 patients were included. Median (Q1 [1st quartile], Q3 [3rd quartile]) age at index was 58 (49, 63) years; 52% were female; 47.2% residents in the South, 26.4% in the Midwest, 14.4% in the East and 12.0% in the West. In terms of healthcare coverage, 64.0% were under commercial, 27.2% self-insured and 8.8% under Medicare plans. Most patients (60.8%) at the start of enco had metastases in 3 or more sites, predominantly in the liver (76.8%), lymph nodes (50.4%), and lung (43.2%). The 2011 Modified Quan Charlson Comorbidity Index was 0 for 44.8% of the patients, 1-2 for 32.5%, and 3 or more for 16.0%. Mean (SD [standard deviation]) number of pre-index treatment regimens was 0.87 (0.73). Among the enco patients who had a previous EGFR claim, 16% had claims, FOLFIRI +/- beva were the most common. Among the ones who had a subsequent treatment computed in claims, FOLFIRI +/- beva was the most common. Conclusions: This study provides current RW demographics, disease characteristics and treatment patterns among BRAF mCRC patients treated with enco in the US. Research Sponsor: Pfizer.
Timing of primary tumor resection after systemic chemotherapy initiation among patients with metastatic colon cancer. First Author: Munir Buhyah, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX.

**Background:** In patients with resectable, metastatic colon cancer, the optimal timing of definitive resection of the primary tumor after initiation of chemotherapy remains unclear. Our goal is to identify factors that influence the interval between chemotherapy and definitive surgical management, and its impact on overall survival. We hypothesize that patients with shorter chemotherapy-to-surgery intervals (less than 60 days or about 2 months) compared to 61-180 days (2-6 months) or greater than 180 days (>6 months), will have the worst overall survival.

**Methods:** We conducted a retrospective analysis of all patients diagnosed with metastatic colon cancer from 2004-2016 who underwent resection of both primary tumor and distant metastatic site from the National Cancer Database (NCDB). Among those who received chemotherapy prior to surgery, we calculated the interval days between initiation of chemotherapy and primary tumor resection. Descriptive analysis, logistic regression, and overall survival was performed comparing patients with chemotherapy-to-surgery intervals of <60, 60-180, and >180 days. Results: A total of 2,238 patients were included, of which 143 (6%), 1,146 (65%), and 649 (29%) were in the <60, 60-180, and >180 days groups, respectively. Similar distribution of patients across groups was observed for age, gender, insurance status, income, education level, distance travel, and Charlson-Deey scores. Poorly differentiated tumors were more frequent in the <60 days group (12% vs 2-9% for other grades, p<0.001) as well as presence of lymphovascular invasion (8% vs 4%, P = 0.006). The odds of receiving care at an academic facility were lower in the <60 days group (OR: 0.52, 95% CI 0.27-0.99). Overall survival was significantly reduced in the <60 days group compared to 60-180 days (HR= 0.502, 95% CI 0.38-0.89). Conclusions: In this retrospective study from a national database, shorter chemotherapy-to-surgery interval (<60 days) was associated with poorly differentiated tumors and lymphovascular invasion. The odds of receiving surgery in <60 days of receiving chemotherapy was lower in academic/research facilities. A reduction in overall survival was observed in the shorter interval (<60 days) group compared to longer intervals. More research is needed to define the optimal chemotherapy-surgery interval and factors that influence this. Research Sponsor: None.

Multisite external validation of blood test for colorectal neoplasia screening in a majority average-risk screening cohort of 449 subjects. First Author: Shai Friedland, Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA.

**Background:** The FirstSight CRC screening blood test was previously shown to have sensitivities of 92.1% and 54.5% for CRC and AA at a specificity of 90.6% for 1,038 subjects from 18 clinics. In this report, we describe the independent external validation of the predefined FirstSight CRC screening blood test from subjects from 16 sites dispersed across the US, 4 of which are new and did not participate in the previous study. Methods: The validation study included subjects from two sources: Average-risk, asymptomatic screening subjects from screening clinics supplemented with diseased-only subjects from surgical oncology centers. Blood was drawn before bowel prep for colonoscopy or treatment. External validation as well as Monte Carlo cross-validation (MCCV) methods were used to evaluate the performance of the pre-defined FirstSight assay, algorithm, and clinical thresholds in this independent external validation set. Results include sensitivity and specificity to detect CRC and AA and 95% confidence intervals. Results: The study cohort (57.2% female; median age 59.9 yrs) consisted of 449 subjects (White 61.7%, Black 14.5%, Hispanic 18%, AAP and Middle Easterners 5%). The majority of them, 376 (84%) were asymptomatic, average-risk screening subjects (including 1 CRC, 53 AA, and all 322 negative subjects). An additional 74 (16%) diseased subjects (19 CRC and 34 AA) were enriched due to low disease prevalence. The FirstSight algorithm derives a test score from 0 to 100 as a quantitative measure of AA and CRC risk with a cutpoint to assign a binary low- or high-risk designation. The previously described cutpoint of 47.2 yielded a test specificity of 90.0%, and 90.0% and 52.9% sensitivity for the detection of CRC and AA, respectively. Here we report a higher cutpoint 50 with identical sensibilities but improved specificity to 90.7%. Point estimates of sensitivity and specificity, including CRC staging, and Clapper-Pearson exact 95% confidence intervals based on the external validation results are presented below. Conclusions: An external validation included 449 subjects from a multi-site, majority average-risk CRC screening study successfully validated the FirstSight Blood Test’s high performance as previously established with 1,038 subjects. The results bring forth confidence in the Test’s reproducibility in a large-scale clinical trial. Clinical trial information: NCT0127096. Research Sponsor: None.

Trends in colorectal cancer screening from NHS survey: Analysis of modalities impact on overall screening. First Author: Derek W. Ebner, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN.

**Background:** Colorectal cancer (CRC) is the second leading cause of cancer-related mortality among men and women combined in the United States (US). Although the national screening rate has increased over the years, it remains below the target of 80%. From 2005 onwards, using Na-

**Methods:** Using National Health Interview Survey (NHIS) data from 2005 onwards, we examined CRC screening (colonoscopy, mt-sDNA, FIT/FIT, sigmoidoscopy) rates among adults aged 50-75 years. A pseudo-time-series cross-sectional (pseudo TSCS) analysis was conducted including random effects Generalized Least Square (GLS) regression model to estimate the relative impact of each modality on the overall increase in CRC rates from 2018 to 2021. Results: Among 50-75 years old individuals, the estimated CRC screening use increased by 32% from 2005 to 2021 (47.7% to 69.9%). Between 2018 to 2021, the rates increased from 64% to 70%, driven largely by increased use of mt-sDNA, a 62.1% increase from 2018 to 2021 (2.5% to 6.6%). During this time period, colonoscopy utilization increased by 4.4% (61.2% to 64.0%), while FOBT/FIT utilization increased by 3.6% (5.3% to 5.5%). A pseudo-TSCS analysis showed that mt-sDNA contributed substantially to the overall CRC screening rate increase during years 2018-2021 (77.3%; P < 0.0001). Conclusions: While CRC screening rates are increasing, they remain below the national goal of 80%. Mt-sDNA as a home-based, non-invasive screening, recommended at a 3-year interval, has been leveraged to improve overall CRC screening rates, particularly to address the screening backlog created during the COVID-19 pandemic. A collaborative approach between healthcare providers and screening-eligible individuals is needed to empower patients with choice for their CRC screening modality to achieve the national goal. Research Sponsor: Exact Sciences, Inc.

Enhanced blood-based colorectal cancer screening with improved performance in detection of early stage disease. First Author: Sven Duenwald, Guardant Health, Redwood City, CA.

**Background:** Blood based colorectal cancer (CRC) screening has been validated for use in average risk populations (ECLIPSE NCT#04136002; Guardant Health, USA). Here we present the performance of an enhanced version of a blood-based screening test developed to optimize detection of low shedding tumors by leveraging epigenomic features of cell-free DNA (cfDNA). Test performance was assessed across screen-relevant individuals from the intended use population, including a collection of screen-detected CRC and enriched cohort of individuals with endoscopy finding of CRC.

**Methods:** We trained a regression model to classify whether aberrant cfDNA originated from individuals with CRC or non-ACN individuals and compared performance to an original model in a fixed set of screen-relevant samples sequenced to a median of 11MB reads per sample across a panel approximately 1MB in size. Model optimization focused on identifying training settings and samples to maximize detection of low shedding screen-relevant tumors and introduced noise reduction techniques to minimize technical variation. The final enhanced model was trained in over 4500 samples; the calling cut-off was set to target 90% specificity in the average-risk population following US-Census age distribution. Analytical Limit of Detection (LoD) was estimated using ~5,000 in silico dilution samples generated from blood samples from 25 CRCs and ~1,650 non-ACNs. Results: This training approach yielded a 2X improvement in the analytical LoD of 0.004 to 0.008 compared to the original model validated in the ECLIPSE trial. The model also yielded an increase in overall CRC clinical sensitivity from 84% to 91%, N=45, with notable sensitivity improvement from 76% to 88% in detecting early localized stage I/II CRC, N = 25, while maintaining specificity at 91%. Conclusions: This enhanced blood-based colorectal cancer screening blood test shows improved performance in early stage CRC detection demonstrating the potential of continuous improvement in the performance of cfDNA-based screening tests powered by data and clinical insights. Research Sponsor: Guardant Health.
Circulating tumor DNA (ctDNA) positivity and its association with clinicopathological characteristics by novel blood-based test for colorectal cancer (CRC) screening from a multi-center large cohort: COSMONE-CRC. First Author: Tatsuro Murano, Department of Gastroenterology and Endoscopy, National Cancer Center East Hospital, Kasai, Japan

Background: Blood-based CRC screening has yielded performance comparable to stool-based screening tests and may be a modality that addresses the adherence gap in CRC screening. To investigate the diagnostic performance and its clinical relevance, we evaluated the test performance of a blood-based CRC screening test in a large cohort of individuals enriched for advanced colorectal neoplasia and early CRCs. Methods: 501 individuals presenting to ten institutions in Japan from 2020 to 2021 for treatment of advanced adenomas (AAs) or CRCs were consented and provided a pre-treatment blood sample (40ml, whole blood in Streck cell-free DNA blood collection tubes). In addition to undergoing surgery or endoscopic resection within 30 days after sample collection and the pathological specimens were reviewed to determine cancer histology and stage, as well as IA histology. Pre-treatment blood samples were analyzed with a multi-modal (genomic and epigenomic) ctDNA CRC detection assay (Shield, Guardant Health, USA). Final ctDNA results were correlated with clinical data to determine the association of clinicopathological characteristics with test sensitivity. This study is registered as a clinical trial under UMIN000037765. Results: 451/501 (90%) individuals met inclusion/exclusion criteria and provided adequate blood samples that passed testing quality control criteria. Median age at consent was 67.4 years (range 31 – 92). 44% were female. 214/451 (47.4%) had a prior positive fecal occult blood test (FOBT). Of individuals with a negative or unknown FOBT testing, 161/237 (68%) had GI symptoms (e.g. abdominal pain, bloody/narrowing stool, constipation/diarrhea). The test identified 88% (288/330) of CRCs, including 49% (33/68) of carcinoma in situ and 24% (9/37) of AAs with high-grade dysplasia. Stage I, 98% (87/89) Stage II, 97% (90/93) Stage III, and 100% (12/12) Stage IV. Overall sensitivity in detecting Stage I-III was 87%. The test identified 37% (54/146) of AAs, in-cluding 49% (33/68) of carcinoma in situ and 24% (9/37) of AAs with high-grade dysplasia. Sensitivity for right-sided CRC was 84% (61/73), 87% (59/68) for left-sided CRC, and 90% (148/164) for rectal stages. Stage I test sensitivity was significantly associated with tumor stage < 1 cm (P < 0.01) and 0.1 cm (P < 0.01), left-sided or rectal tumor location (P < 0.05), and tumor depth in univariate analysis, whereas the tumor depth (T2) was the sole factor associated with test positivity (P < 0.05) in multivariate analysis. Specificity on this assay is 90% as determined in the ECLIPSE clinical study (NCT04136002). Conclusions: This study evaluated the performance of a blood-based test for CRC and its clinicopathological relevance in a large-scale cohort. In this population enriched for early colorectal neoplasia, the sensitivity was 88% for CRC and 37% for AAs. This performance is consistent with previous reports. Clinical trial information: UMIN000037765. Research Sponsor: Guardant Health.

Colorectal Cancer Alliance: Promoting prevention and early detection with screening navigation and a personalized recommendation via a digital screening quiz tool for colorectal cancer. First Author: Kim Newcombe, Colorectal Cancer Alliance, Washington, DC.

Background: Evaluating the effectiveness of a Colorectal Cancer screening navigation model delivered in a digital platform offered by a patient advocacy organization. Designed as a digital screening quiz tool and live navigation to promote CRC screening, the Colorectal Cancer Alliance’s Screening Quiz is a risk stratification tool that connects respondents to live certified cancer care navigators delivering evidence-based interventions, the Alliance will continue to leverage the Screening Quiz in part-nership with healthcare and community stakeholders to close Colorectal Cancer screening gaps. Research Sponsor: None.

Comprehensive analysis of differentially methylated regions in colorectal cancer (CRC). First Author: Omid Solami, Natera, Inc., San Carlos, CA.

Background: Epigenetic alterations have been shown to govern many disease states, including cancer. A key epigenetic mark is the DNA methylation of CpGs. Large studies, like The Cancer Genome Atlas, have shown that DNA methylation can differentiate cancer subtypes and help to predict patient outcomes. However, defining regions enriched for advanced colorectal neoplasia and early CRCs provides a method to identify cell-free DNA (cfDNA) methylation-based partitioning to identify cancer related genomic alterations and epimorphic modifications (methylation and modifications in chromatin state). Results are integrated to yield a binary ‘positive’ or ‘negative’ result. Here we present findings correlating the blood-based test results with colonoscopy findings and find from available 1-year follow-up data. Results: 556 out of 598 eligible individuals had an evaluable colonoscopy and a blood-based test result that passed quality control standards. Of the 556 individuals, 52% were female; median age was 55 years. Average test positivity (92%). 44% were female. 214/451 (47%) had a prior positive fecal occult blood test (FOBT). Of individuals with a negative or unknown FOBT testing, 161/237 (68%) had GI symptoms (e.g. abdominal pain, bloody/narrowing stool, constipation/diarrhea). The test identified 88% (288/330) of CRCs, including 49% (33/68) of carcinoma in situ and 24% (9/37) of AAs with high-grade dysplasia. Sensitivity for right-sided CRC was 84% (61/73), 87% (59/68) for left-sided CRC, and 90% (148/164) for rectal stages. Stage I test sensitivity was significantly associated with tumor size < 1 cm (P < 0.01) and 0.1 cm (P < 0.01), left-sided or rectal tumor location (P < 0.05), and tumor depth in univariate analysis, whereas the tumor depth (T2) was the sole factor associated with test positivity (P < 0.05) in multivariate analysis. Specificity on this assay is 90% as determined in the ECLIPSE clinical study (NCT04136002). Conclusions: This study evaluated the performance of a blood-based test for CRC and its clinicopathological relevance in a large-scale cohort. In this population enriched for early colorectal neoplasia, the sensitivity was 88% for CRC and 37% for AAs. This performance is consistent with previous reports. Clinical trial information: UMIN000037765. Research Sponsor: Guardant Health.

Prospective study of a multi-modal blood-based test for colorectal cancer screening. First Author: Paloma Peinado, Department of Medical Oncology, Centro Integral Oncologico Clara Campal, Hospital HM Sanchinarro, HM Hospitals, Spain/ Department of Medical Clinical Sciences, Facultad de Medicina, Universidad Camilo José Cela, Madrid, Spain.

Background: Colorectal cancer (CRC) screening has proven to be a useful tool for the detection and prevention of CRC. However, adherence is low despite the multiple screening options available. A blood-based CRC screening test with optimized sensitivity and specificity may improve screening adherence. We aimed to prospectively evaluate the performance of a multimodal blood-based colorectal neoplasia screening test in individuals presenting for colonoscopy. Methods: This prospective, observational study was developed in four hospitals in Spain and enrolled individuals (45 – 84 years of age) undergoing a colonoscopy procedure (including diagnostic and screening colonoscopies), between March 2020 and September 2021. Eligible individuals consented to use of medical records for research and to provide a blood sample prior to colonoscopy procedure. Individuals were followed for one year. Whole blood was collected and shipped ambient to a central laboratory for analysis (Shield, Guardant Health, Redwood City, CA, USA). The blood-based colorectal neoplasia test is a 50kb next-generation sequencing based panel and bioinformatic platform that incorporates cell-free DNA (ctDNA) methylation-based partitioning to identify cancer related genomic alterations and epimorphic modifications (methylation and modifications in chromatin state). Results are integrated to yield a binary ‘positive’ or ‘negative’ result. Here we present findings correlating the blood-based test results with colonoscopy findings and find from available 1-year follow-up data. Results: 556 out of 598 eligible individuals had an evaluable colonoscopy and a blood-based test result that passed quality control standards. Of the 556 individuals, 52% were female; median age was 55 years. Average test positivity (92%). 44% were female. 214/451 (47%) had a prior positive fecal occult blood test (FOBT). Of individuals with a negative or unknown FOBT testing, 161/237 (68%) had GI symptoms (e.g. abdominal pain, bloody/narrowing stool, constipation/diarrhea). The test identified 88% (288/330) of CRCs, including 49% (33/68) of carcinoma in situ and 24% (9/37) of AAs with high-grade dysplasia. Sensitivity for right-sided CRC was 84% (61/73), 87% (59/68) for left-sided CRC, and 90% (148/164) for rectal stages. Stage I test sensitivity was significantly associated with tumor size < 1 cm (P < 0.01) and 0.1 cm (P < 0.01), left-sided or rectal tumor location (P < 0.05), and tumor depth in univariate analysis, whereas the tumor depth (T2) was the sole factor associated with test positivity (P < 0.05) in multivariate analysis. Specificity on this assay is 90% as determined in the ECLIPSE clinical study (NCT04136002). Conclusions: This study evaluated the performance of a blood-based test for CRC and its clinicopathological relevance in a large-scale cohort. In this population enriched for early colorectal neoplasia, the sensitivity was 88% for CRC and 37% for AAs. This performance is consistent with previous reports. Clinical trial information: UMIN000037765. Research Sponsor: Guardant Health.

Research Sponsor: None.
Clinicopathologic characteristics of patients with early-onset colorectal cancer. First Author: Maki Takagi, Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

Background: Although the incidence of colorectal cancer has been declining in the United States in recent years, the incidence of young patients under 50 years of age has been reported to be increasing by several percent per year. Various studies have been conducted to characterize early-onset colorectal cancer (EO-CRC); however, it has been unclear whether it is a different entity from late-onset colorectal cancer (LO-CRC). In this study, we evaluated the clinicopathologic characteristics of EO-CRC in Japan.

Methods: This study included 1,336 patients who underwent surgical resection for colorectal cancer at Tokyo Metropolitan Komagome Hospital from January 2015 to December 2019. We performed genetic testing for patients with suspected Lynch syndrome after providing genetic counseling and obtaining informed consent. The study protocol was approved by the Institutional Review Board.

Results: Of the 1,336 colorectal cancer patients, 117 (8.9%) had EO-CRC with a median age at diagnosis of 44 (17–49) years. Tumors were located at right-sided colon in 23 patients and left-sided colorectum in 92 patients with EO-CRC, respectively. The clinical stage of the tumor was I in 19, II in 23, III in 50, and IV in 23 patients with EO-CRC, respectively. Histologically, differentiated type, undifferentiated type, and mucinous carcinoma were 106, 5, and 3 patients, respectively. KRAS mutation was detected in 25.0% and BRAF V600E was detected in 4.3% of patients with EO-CRC. In the microsatellite status, MSI-High was detected in 6 (5.1%) patients with EO-CRC, of whom 3 (2.6%) were diagnosed with Lynch syndrome by genetic testing. Cause gene was MLH1 in 2 patients and MSH2 in one patient. In hereditary tumors, 2 patients with familial adenomatous polyposis were included in addition to Lynch syndrome. On the other hand, 1,219 (91.2%) had LO-CRC with 34.5% of KRAS mutation and 6.4% of BRAFV600E. MSI-High was detected in 69.5% patients with LO-CRC, of whom 0.4% were diagnosed with Lynch syndrome. Lynch syndrome was significantly more common in EO-CRC (p=0.026).

Conclusions: The alterations of KRAS and BRAF tended to be more frequent in EO-CRC. The frequency of hereditary CRC was more frequent in EO-CRC than in LO-CRC. Research Sponsor: None.

Genetic testing of Japanese patients with serrated polyposis syndrome: A multicentric study. First Author: Akinari Takado, Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

Background: Serrated polyposis syndrome (SPS) is a rare condition associated with an increased risk of colorectal cancer. Previous studies have identified germline truncating variants of the RNF43; however, patients harboring these variants comprise a small part of those with SPS, in most of whom the causative gene remains unknown. To date, no study has described the genetic features of Japanese patients with SPS. The present study aimed to identify candidate causative genes of SPS in Japanese patients.

Methods: Captures for equal to or more than 55 gene regions were performed using Agilent HaloPlex or Ion AmpliSeq technologies in SPS patients enrolled in The Study Group for Establishment of Diagnosis of Hereditary Gastrointestinal Tract Cancer Syndromes Based on a Next-Generation Sequencing Technology (SGHGCS). Whole exome sequencing of tumor tissues was performed whenever candidate gene was identified. Results: Eleven patients (four males, seven females) were enrolled. Of these, nine had a history of colorectal cancer; four had a family history of colorectal cancer; and two had a family history of polyposis. Genetic testing identified two variants of VUS, POLG1 c.670C>T (p.R224C) and BRCA2 c.4167T>G (p.L1390W). Additionally, a nonsense variant, BUB1 c.1543G>T p.Q515St was deemed likely to be pathogenic. The patient with the BUB1 variant was 47-year-old female with transverse colon cancer with more than 50 serrated polyps. She was a non-smoker. The variants detected in the transverse colon cancer did not include the canonical variants in common colorectal cancer, such as APC, KRAS or TP53 and were mostly transition substitutions (C>T). Conclusions: BUB1 was identified as a novel candidate causative gene of SPS in a patient with SPS with no smoking habit. These findings will hopefully contribute to our understanding of the genetic basis of SPS. Research Sponsor: None.
Impact of revising colorectal cancer screening guidelines on health care resources in Canada. First Author: Brendan Chia, BCCA, Vancouver Cancer Centre, Vancouver, BC, Canada

Background: The rising incidence of early-onset colorectal cancer (CRC) has prompted U.S. organizations to lower the recommended CRC screening age for average risk adults from 50 to 45 years old, while Canadian programs remain unchanged. Canadian guidelines also differ from the U.S. in preferentially screening with a fecal immunochemical test (FIT) and recommend against performing colonoscopies as a screening test. Differences in national healthcare administration warrants investigation into the resource impact of updating screening guidance in Canada.

Methods: Microsimulation modeling was performed using OncoSim (Version 3.6) to project health and economic outcomes of different CRC screening strategies based on Canadian population data. Four simulated birth cohorts of the Canadian population born between 1973–1992 were tracked for a 40-year span from the year the oldest in each cohort turned 40 until the youngest in the same cohort turned 75.Colorectal adenoma rates were adjusted according to cohort risk ratios estimated from historical incidence data to reflect real-world CRC screening outcomes. Outcomes were reported for the cumulative cohort. Results: Compared to FIT screening at age 50, FIT screening at 45 reduced deaths by 5,220, incidence by 11,980, and added 96,100 health-adjusted life years (HALY). Colonoscopy screening at age 45 led to 17,870 fewer deaths, 74,250 fewer cases and added 314,960 HALYs. FIT and colonoscopy screening at age 45 had incremental costs of CAD$23,529 and $57,881 per HALY gained vs. a FIT at age 50, respectively. Across screening strategies, the greatest benefits were observed in the youngest cohort. Colonoscopy screening at age 45 resulted in 10,679,540 more total colonoscopies than the current capacity of 8,966,979 with FIT screening at age 50. Lowering the screening age to 45 with a FIT increased colonoscopy demand by 329,555. The total cost of CRC care (screening, diagnosis and treatment) increased with lower screening ages and colonoscopy first modalities, while the cost of CRC management (diagnosis and treatment) decreased with lower screening ages and colonoscopy first approaches. Conclusions: Adjusting current CRC screening guidelines demonstrates significant resource implications with proportional health benefits. Lower screening ages and colonoscopy first approaches have the largest resource demand and greatest health outcomes, while the incremental cost per HALY gained for all screening strategies is modest compared to standard benchmarks. Research Sponsor: None.

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**Poster Session**

**COLORECTAL CANCER**

**82**

**Poster Session**

**COLONTOWN** Searching Safari: Education to remove barriers to pursue clinical trials for patients with metastatic colorectal cancer (mCRC). First Author: Julie Clauer, Paltown/Colontown, Burbank, CA

**Background:** Clinical trials can expand otherwise limited treatment options for patients with metastatic cancer. Yet, the complexity of the trial landscape can prevent patients from pursuing trials. Even in mCRC patients motivated to participate in trials, 79% described trial search negatively, mainly overwhelming. We hypothesized that “clinical trial literacy” and familiarity with mCRC processes of pursuing trials were critical predictors of patients’ trial interest. To test this, we, as managers of COLONTOWN, a large, online CRC patient/caregiver community, developed an interactive course.

**Methods:** We reviewed many posts from the COLONTOWN clinical trial groups to identify gaps between the desire to participate in a trial and the knowledge/tools/needs to do so. We then determined those most critical to benefit all mCRC MSS patients interested in trials, but not in urgent need of trials. We developed a 4-week long course with 5 hours of live online sessions and 5 hours of homework. Participants built fluency in the language of clinical trials, learned about available tools, and identified and addressed trials in the context of their personal needs and disease dynamics. Unlike most trial resource trials, the focus was on informed patient-centered decision-making, not on the science or mechanics of trials. The course was offered 3 times in 2022/23 with iterative improvements after each session. Participants (n=48) were assessed for their attitudes around trials before and after the course to measure impact. Results: We found that our repeatable, scalable course improves mCRC patient perceptions of and skills to pursue trials as evidenced by pre-post course surveys. This included average response to “How prepared do you feel to find a clinical trial” increasing from 2.1 to 3.8 on a 5-point scale and positive sentiment about the process rising from 7% to 71% (table). Positive feedback on meeting course objectives and amount of coursework being ‘just right’ (96% and 92% of responses, respectively) support the material’s value for time invested.

**Conclusions:** Through systematic skill building, self reflection, and practical tools, our guided course can build confidence and empower patients and caregivers to take the next step to pursue clinical trials. Patient education can indeed help overcome often overlooked emotional and knowledge barriers to pursuing clinical trials present even in a motivated patient population. Next, we plan to create and assess the benefit of an additional on-demand e-learning course and to expand to other patient groups. Research Sponsor: None.

**Patient perceptions of clinical trials.**

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**Preparedness to find a trial?**

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<tr>
<th>Preparedness to find a trial?</th>
<th>Pre-Course</th>
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<th>%</th>
<th>Post-Course</th>
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<td>100%</td>
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**Likelihood to pursue a trial?**

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<th>Pre-Course</th>
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<th>%</th>
<th>Post-Course</th>
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<td>N</td>
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84  

**Poster Session**

**Local excision to enhance organ preservation in rectal cancer after favorable preoperative response to total neoadjuvant therapy.** First Author: Aron Bercz, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Total neoadjuvant therapy (TNT) for rectal cancer (RC) can achieve clinical complete response in up to 85% of patients. For patients with locally advanced rectal cancer, the use of LE as an important adjunct to WW management. Research Sponsor: National Research Council.

**Methods:** We conducted a retrospective chart review of 234 RC patients who received adjuvant CAPOX or FOLFOX between January 2021 and December 2022. Pts with rectal cancer requiring neoadjuvant chemotherapy or radiotherapy were excluded. Demographic, tumor, and treatment information was collected. High-risk features were defined as pT4 or pN2 tumors. “Urban” setting was defined based on the population size of the regional health authority. Descriptive statistical analyses were performed to examine baseline characteristics and Fisher’s exact test was used to examine binary associations.

**Results:** 242 pts were included, of which 234 (52%) and 218 (48%) were planned to receive 3 and 6 mos of ACT respectively (see table). Within the 3 mos group, 226 (97%) received CAPOX. Within the 6 mos group, there was a 51%/49% split between CAPOX/FOLFOX. By univariate analysis, factors associated with 3 mos of CAPOX vs 6 mos of ACT were age >70y (P=0.039), low/intermediate grade (P=0.005) and low-risk stage III disease (P=0.0001). 29% of pts planned for 6 mos of oxaliplatin ACT had low disease, with 52% of these receiving CAPOX.

**Conclusions:** 3 mos of adjuvant CAPOX is an accepted option for nearly all pts with stage III disease with consequent less morbidity and fewer treatment visits. In this contemporary cohort, use of 3 mos of adjuvant CAPOX remains low and is associated with older age and low-risk disease. 6 mos of oxaliplatin is still being offered to pts with low disease. Exploration of patient preferences, real-world treatment and time toxicities, and resource costs may improve more widespread adoption of 3 mos of adjuvant CAPOX in stage III CRC. 

**85  

**Poster Session**

**Real-world adoption of 3 months of adjuvant oxaliplatin chemotherapy in patients with stage III colorectal cancer (CRC).** First Author: Tharani Krishnan, BC Cancer - Vancouver, Vancouver, BC, Canada

**Background:** Based on the IDEA analysis, 3 months (mos) of adjuvant chemotherapy (ACT) with CAPOX has emerged as an option for both low-risk and high-risk stage III CRC. This has resource utilization, cost and toxicity benefits (particularly less neurotoxicity) without compromising efficacy. This study examines the patterns of uptake of CAPOX vs FOLFOX and duration of ACT in a contemporary cohort of patients with stage III CRC in the province of British Columbia (BC), Canada. **Methods:** The provincial pharmacy database was used to identify pts with resected stage III CRC who received adjuvant CAPOX or FOLFOX between January 2021 and December 2022. Pts with rectal cancer requiring neoadjuvant chemotherapy or radiotherapy were excluded. Demographic, tumor, and treatment information was collected. High-risk features were defined as pT4 or pN2 tumors. “Urban” setting was defined based on the population size of the regional health authority. Descriptive statistical analyses were performed to examine baseline characteristics and Fisher’s exact test was used to examine binary associations.

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**Characteristic n (%)**

<table>
<thead>
<tr>
<th>Total Cohort (n=452)</th>
<th>3 Months CAPOX Planned (n=226)</th>
<th>6 Months CAPOX Planned (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>254 (56.2)</td>
<td>119 (52.7)</td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>314 (69.5)</td>
<td>147 (65.0)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>138 (30.5)</td>
<td>79 (35.1)</td>
</tr>
<tr>
<td>Union setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>262 (58.1)</td>
<td>118 (51.9)</td>
</tr>
<tr>
<td>Rural</td>
<td>190 (41.8)</td>
<td>98 (43.3)</td>
</tr>
<tr>
<td>Right colon</td>
<td>214 (47.3)</td>
<td>108 (47.0)</td>
</tr>
<tr>
<td>Left colon</td>
<td>207 (45.3)</td>
<td>102 (45.1)</td>
</tr>
<tr>
<td>Histological grade</td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td>131 (29.0)</td>
<td>67 (29.6)</td>
</tr>
<tr>
<td>Low/intermediate</td>
<td>384 (86.6)</td>
<td>202 (91.0)</td>
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<tr>
<td>High-risk stage III:</td>
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<td></td>
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<tr>
<td>T4</td>
<td>198 (43.3)</td>
<td>97 (42.6)</td>
</tr>
<tr>
<td>pN2</td>
<td>131 (29.0)</td>
<td>63 (27.8)</td>
</tr>
<tr>
<td>Seen surg onc prior to med onc</td>
<td>122 (27.0)</td>
<td>64 (28.0)</td>
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</table>

51% more likely to occur when patients were seen by medical oncology prior to surgery and patients who saw both surgical and radiation oncology prior were significantly less likely to pursue a trial. Discussion: The time from cancer diagnosis to treatment initiation was not significantly different between patients who were and were not seen by the surgeon and radiation oncologist prior to the medical oncologist (56 vs. 55 days respectively), nor if MCC discussions were or were not required (55 vs. 55 days). However, almost half of all patients (93, 46%) required an additional pre-treatment visit with their medical oncologist, and patients who saw both surgical and radiation oncology prior were significantly less likely to require additional pre-treatment visits with medical oncology (25% vs. 61%; p<0.0001). Conclusions: The time from cancer diagnosis to treatment initiation was not significantly impacted by the order of specialist consultations with the multidisciplinary team, nor if patients required MCC discussion or additional pre-treatment visits with medical oncology. However, additional pre-treatment visits with medical oncology were significantly more likely to occur when patients were seen by medical oncologist prior to surgery and/or radiation oncology, representing a logistical and financial inefficiency in the system, and a potential area for process improvement. Research Sponsor: None.
86  Post Session

Retrospective review of compliance with guideline-directed germline testing in microsatellite instability-high colorectal cancer treated at the Veterans Health Administration. First Author: Karly Williams Silva, University of Washington, Seattle, WA

Background: Lynch syndrome (LS) is an autosomal dominant inherited cancer syndrome that confers an increased risk of colorectal cancer (CRC). As clinical and historical features under-recognize LS cases (3-5% of CRC), universal screening of CSRs for LS is recommended. Patients whose CSRs are mismatch repair protein deficient (dMMR) and/or microsatellite instability high (MSI-H) are recommended to have subsequent genetic evaluation to screen for germline mutations. Confirmed LS cases change surveillance recommendations for affected patients and their relatives. Within Veterans Health Administration (VHA), GT is ordered by genetic counselors at genomics medicine tel- ehealth centers (GMTC), after initial consultation. We aim to quantify rates at which CRC patients treated at the VHA complete germline testing (GT) when indicated.

Methods: The electronic health records (EHRs) of VHA patients with known dMMR/MSI-H CRC were reviewed. Cases were extracted from both Veterans Affairs (VA) Puget Sound and referral VA MSI testing laboratories. Surgical pathology reports and clinical documentation were reviewed in Joint Longitudinal Viewer (JLV) to determine if GT was indicated and reason for non-testing, if not performed. Patients with known LS prior to development of CRC were excluded, and patients with dMMR in MLH1 or MSI-H with concurrent BRAF/V600 mutation and/or MLH1 hypermethylation were considered to have sporadic CRC.

Results: Of 110 patients with abnormal tumor LS screening, 39 (36%) patients’ tumor tissue underwent IHC for dMMR, 16 (14%) underwent PCR for MSI, and 55 (50%) had both. 45 (41%) patients were classified as somatic MSI-H. 65 (59%) patients met criteria for referral for GMTC and GT. Of these 65, 49 (75%) underwent GMTC and 16 (25%) did not undergo GT and 16 did, which confirmed 4 cases of LS and revealed 1 variant of uncertain significance in the MLH1 gene. Reasons for non-testing were: 7 (14%) declined all cancer testing and treatment after CRC diagnosis or were lost to follow-up/declined establishment of care, 3 (6%) declined referral to GMTC and 14 (28%) accepted referral to GMTC but never had consultation, 7 (14%) accepted referral to GMTC but declined GT when offered, and 18 (37%) were never offered GT referral or GT.

Conclusions: A majority of dMMR/MSI-H cases with an indication for GT were referred for genetic counseling, but only a small subset completed testing. This analysis identified multiple areas for improvement, including lack of recognition by healthcare providers for the need for GT, and lack of completion of testing by patients at multiple levels. Further evaluation of VHA-specific barriers is needed to improve the quality of delivered care. Research Sponsor: None.

88  Post Session

Angiotensin receptor blockers and severe diarrhea and/or enterocolitis induced by CAPOX in patients with colorectal cancer: A multicenter cohort. First Author: Adriano Fernandes Fernandes Teixeira, Clinica AMO, Vitoria Da Conquista, Brazil

Background: While patients (pts) with colorectal cancer (CRC) treated with CAPOX (capecitabine and oxaliplatin) may experience severe diarrhea, risk factors for this toxicity remain underdetermined. We have previously shown that concurrent use of angiotensin receptors blockers (ARB), a known inhibitor of TGF-B which is important for the development of CRC were excluded, and patients with dMMR in MLH1 or MSI-H with concurrent BRAF/V600 mutation and/or MLH1 hypermethylation were considered to have sporadic CRC. Results: Of 110 patients with abnormal tumor LS screening, 39 (36%) patients’ tumor tissue underwent IHC for dMMR, 16 (14%) underwent PCR for MSI, and 55 (50%) had both. 45 (41%) patients were classified as somatic MSI-H. 65 (59%) patients met criteria for referral for GMTC and GT. Of these 65, 49 (75%) underwent GMTC and 16 (25%) did not undergo GT and 16 did, which confirmed 4 cases of LS and revealed 1 variant of uncertain significance in the MLH1 gene. Reasons for non-testing were: 7 (14%) declined all cancer testing and treatment after CRC diagnosis or were lost to follow-up/declined establishment of care, 3 (6%) declined referral to GMTC and 14 (28%) accepted referral to GMTC but never had consultation, 7 (14%) accepted referral to GMTC but declined GT when offered, and 18 (37%) were never offered GT referral or GT.

Conclusions: A majority of dMMR/MSI-H cases with an indication for GT were referred for genetic counseling, but only a small subset completed testing. This analysis identified multiple areas for improvement, including lack of recognition by healthcare providers for the need for GT, and lack of completion of testing by patients at multiple levels. Further evaluation of VHA-specific barriers is needed to improve the quality of delivered care. Research Sponsor: None.

87  Post Session

Associations of postdiagnosis changes in physical activity with overall mortality among patients with stage I-IIA colorectal cancer. First Author: Karel Conraads, Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands

Background: Several observational studies show an association between physical activity (PA) at diagnosis and reduced risk of mortality among colorectal cancer (CRC) patients, but there has been limited research examining the potential benefit of changes in PA levels after CRC diagnosis. Here we investigate the association between change of PA and all-cause mortality in patients with stage I-IIA CRC receiving resection with curative intent.

Methods: Data were used from two large Dutch CRC cohort studies (PLCRCR & COLON), which assessed PA at diagnosis (T0), six (T6) and twelve (T12) months after diagnosis, using the SQUASH questionnaire. A total of 2540 stage I-IIA CRC patients with repeated PA measures (i.e. a T0 and at least a T6 or T12 questionnaire) were used for this analysis. Total PA was quantified by calculating Metabolic Equivalent Task (MET) hours per week and categorized as low, moderate, and high PA, based on tertiles of an age- and sex-matched sample of the general population. PA changes were evaluated at T6 and T12 relative to T0. Being active was defined per timepoint as being in the moderate or high total PA group, or adhering to the PA guideline (minimum of 150 minutes per week of moderate-intensity PA). Cox proportional hazards models were used to study the association between PA variables and all-cause mortality, adjusted for age, sex, BMI, and tumor location (colorectal vs rectum). Results: Median follow-up time was 35 months (interquartile range 19–55) during which a total of 133 deaths occurred. Being active at both T0 and T6 compared to being inactive at these timepoints, was associated with a lower rate of all-cause mortality for both PA variables (adjusted hazard ratio (HR) 0.39 [95% confidence interval 0.24-0.65] and 0.41 [0.23-0.72] for total PA and guideline adherence, respectively). Similar results were found when comparing T12 to T0 (being active according to total PA HR 0.20 [0.09-0.42] and guideline adherence HR 0.31 [0.14-0.72]). Changing to either activity or inactivity at T6 or T12 was not significantly associated with all-cause mortality (Table). Conclusions: Maintaining a physically active lifestyle following surgery for stage I to II CRC is associated with improved overall survival, reinforcing the recommendations for physical activity. Research Sponsor: None.

89  Post Session

Oxaliplatin desensitization in patients with GI malignancies: Experience from a tertiary cancer center. First Author: Jacqueline Connell, The Christie NHS Foundation Trust, Manchester, United Kingdom

Background: Oxaliplatin hypersensitivity is not uncommon in patients with gastrointestinal (GI) cancers receiving chemotherapy. The use of oral premedications (dexamethasone, chlorphenamine and famotidine) 30 minutes before treatment and the gradual administration of oxaliplatin over 6.5 hours in four separate escalating doses (desensitisation protocol) is commonly used in such cases. While desensitisation is an option, especially in severe cases, responses and survival outcomes upon rechallenge are not well described.

Methods: A retrospective chart review of patients with various GI malignancies who received oxaliplatin-based desensitisation chemotherapy after a severe drug reaction between October 2019 and October 2022 at a single cancer centre was performed. Clinico pathological characteristics and oncological outcomes were assessed. Results: Forty-four patients with a median age of 61 years (range 38-81) were included. The majority had a diagnosis of CRC (n=22, 50%), followed by oesophago-gastric (n=19, 4%), appendiceal (n=1), cholangiocarcinoma (n=1), and cancer of unknown primary (n=2). More than two thirds of patients (n=32, 73%) were treated with palliative intent. The most common regimens associated with oxaliplatin hypersensitivity reactions after a median of 3 cycles (range 1-10) were FOLFOX (n=24, 55%), CAPOX (n=18, 41%), FLOT (n=1) and FOLFOXIRI (n=1). Seven patients (16%) had another reaction after desensitisation, leading to discontinuation of treatment. Thirty-seven patients (84%) completed treatment as planned. Treatment outcomes after desensitisation included 5 (11%) patients with no evidence of disease (NED) after adjuvant treatment, 16 (37%) patients with stable disease (SD), and 3 (7%) patients with disease progression (PD). Conclusions: Oxaliplatin desensitisation is feasible with low discontinuation rates and leads to acceptable oncological outcomes. All patients should be offered desensitisation to allow continuation of active systemic therapy. Research Sponsor: None.

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A single-institution experience of acute toxicities in patients treated with short course hypofractionated radiotherapy in locally advanced rectal cancer.

First Author: Katie Nadine Lee, Harvard Radiation Oncology Program, Boston, MA

Background: Hypofractionated short course radiation treatment (SCRT) as part of a total neoadjuvant treatment (TNT) approach to treat rectal cancer has increased in popularity since the publication of the RAPIDO trial. However, the literature on SCRT for rectal cancer has not reported significant acute toxicities in the weeks immediately following the completion of treatment. This study examines the acute toxicities in patients treated with hypofractionated radiation therapy as part of their definitive treatment for rectal cancer.

Methods: All patients who were retrospectively analyzed 71 patients with locally advanced rectal cancer treated between 2016-2022 with SCRT (25 Gy in 5 fractions) as part of definitive treatment. Acute toxicity caused by radiation was defined as that occurring from the start of radiation treatment to either 30 days post radiation completion, the start of chemotherapy, or date of surgery, whichever occurred first. Acute toxicity included: tenesmus, paroxysmal rectal pain, rectal bleeding, mucosal ulcers, loose stool, diarrhea, nausea, vomiting, skin rash, or ulceration.

Results: A total of 153 patients were included in the analysis, with a median age of 61 years (range 32-84). Among them, 49% were female, 78.4% had stage III CRC, and the remaining had stage II disease. The racial distribution was White and 17.5% Black. The proportion of patients who completed all planned SCRT doses was 55.5% (85/153) in the entire cohort and 38% (23/60) in patients aged 65 and above (p = 0.22). Among patients intended to receive 4 cycles of CAPOX, only 57% (37/65) completed all 4 cycles. Female patients were less likely to complete treatment than male patients (p = 0.01). Dose reductions for oxaliplatin and capcitabine were observed in 37% (57/153) and 39% (59/153) of patients, respectively. Hospitalizations related to CAPOX-induced toxicities occurred in 18% (27/153) of patients, and 31% (47/153) experienced grade 3 or higher adverse events. A switch to FOLFOX was observed in 5% (8/153) of patients. Conclusions: This study highlights that a substantial number of patients with localized CRC undergoing curative-intent treatment with CAPOX do not complete the planned courses, potentially impacting their overall survival. Moreover, a significant proportion of patients experience grade 3 or higher toxicities with CAPOX, necessitating hospital admissions. These findings underscore the need for careful patient selection and management strategies to optimize the therapeutic benefits of CAPOX in this setting. Research Sponsor: None.

Safety and efficacy of ONO-4578 plus nivolumab in metastatic colorectal cancer.

First Author: Akihito Kawazoe, Department of Gastroenterology and Gastro- intestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: The prostaglandin E2-EP4 signaling is involved in immunosuppression in cancers. In the dose escalation part of the ONO-4578-01, open-label, uncontrolled phase 1-2 study, ONO-4578 plus nivolumab showed manageable safety profile and antitumor activities in metastatic or advanced solid tumors. CRC cohort assessed safety, preliminary efficacy, and biomarkers of 4578+NIV in patients with metastatic colorectal cancer (mCRC). Methods: The CRC cohort was conducted at 12 sites in Japan and it included patients aged ≥20 years with mCRC, those with major organ involvement and primary lesion in the colon or rectum. All patients enrolled: 24 (47.1%) were male and the median age was 59.0 (range, 33-79) years. Adverse events (AEs) occurred in 48 patients (94.1%), wherein grade 3-4 AEs occurred in 23 (45.1%). No patients died due to AEs. Serious AEs occurred in 11 (21.6%) patients. The most common AEs of any grade were rash (33.3%) and anemia (31.4%). Any-grade grade ≥3 treatment-related AEs (TRAEs) occurred in 36 (70.6%) and 13 (25.5%) patients, respectively. Two patients achieved partial response and 16 had stable disease; the objective response rate was 3.9% (90% confidence interval [CI], 0.7–11.8) and the disease control rate was 39.2% (90% CI, 27.7–51.7). The median progression-free survival and overall survival (OS) were 1.54 (90% CI, 1.41–2.79) and 10.68 months (90% CI, 6.67–not reached [NR], respectively. The proportion of patients continuing treatment and OS in subgroups of different PD-L1 combined positive scores (CPS) showed a tendency toward favorable efficacy in CPS-positive subgroups: the proportion of patients continuing treatment for 6 months was 4.5% (1/22) in those with CPS of 0 vs 20% (5/25) in those with CPS ≥1, and the median OS was 9.4 months (90% CI, 5.65–12.06) in those with CPS of 0 vs NR (90% CI, 10.41–NR) in those with CPS ≥1. In CPS ≥1 patients, 4578+NIV showed manageable safety profile and antitumor activity in patients with mCRC. Favorable efficacy was observed in the PD-L1 CPS-positive subpopulation. Clinical trial information: JRCT2008223441. Research Sponsor: Ono pharmaceutical Co., LTD.
Efficacy and safety of LY3537982, a potent and highly selective KRAS G12C inhibitor in KRAS G12C-mutant GI cancers: Results from a phase 1 study. 

First Author: Antoine Hollebecque, Gustave Roussy, Villejuif, France

Background: LY3537982 is an oral, potent, and highly selective inhibitor of GPR-bound KRAS G12C with unique pharmacologic properties that achieve high target occupancy at low absolute exposures. Here we present results of GI tumors treated on LDXX-RAS-20001, a phase 1 study of LY3537982 in patients (pts) with a KRAS G12C mutation. Methods: Dose escalation followed a mTPI-2 method. Dose escalation included a combination with cetuximab in colorectal cancer (CRC). All pts were KRAS G12C inhibitor naive. Key objectives were to determine the RP2D, safety, PK, and antitumor activity per RECIST v1.1. Results: As of 24 July 2023, 73 pts with CRC (32), PAN (24), BTC (10), and other GI tumors (7) were treated with 50-200 mg BID LY3537982. Median age was 62 yrs (range, 38-85) and median number of prior lines of therapies was 3 (range, 0-11). No DLTs were observed. Grade 1 diarrhea was the highest frequency TEAE regardless of attribution (33%). At a median time on treatment of 4 months (range, 0.1-18), 20 pts are ongoing and 53 pts discontinued treatment. In the combination cohort, 46 pts with CRC treated with 100 or 150 mg BID LY3537982 and cetuximab. Median age was 57 yrs (range, 35-77) and median number of lines of prior therapies was 3 (range, 1-8). 1 pt at 100 mg BID had a DLT (ALT/AST increased) and required a dose reduction. TEAEs ≥30%: dermatitis acneiform (59%), diarrhea (44%), dry skin (44%), hypomagnesemia (33%), and fatigue (30%). Vomiting, pruritus, skin fissures, headache, nausea, pyrexia, and rash were mostly grade 1 with 20-24% occurrence. At a median time on treatment of 6 months (range, 0.6-17), 37 pts are ongoing and 9 discontinued treatment (none due to AE). Table shows efficacy data. Conclusions: In pts with GI tumors, LY3537982 alone or in combination with cetuximab demonstrated preliminary efficacy and a favorable safety profile. Clinical trial information: NCT04956640. Research Sponsor: Lexo Oncology, Inc. on behalf of Eli Lilly and Company.

Fruquintinib with PD-1 inhibitors versus TAS-102 with bevacizumab in late-line mCRC: A retrospective cohort study based on propensity score matching. First Author: Rongrong Li, Department of Medical Oncology Gastro- and Urology, Hunan Cancer Hospital, Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan, China

Background: Fruquintinib with PD-1 inhibitors (FP) and TAS-102 with bevacizumab (TB) are two common therapies for patients with previous-treated metastatic colorectal cancer (mCRC). However, it’s still not clear that which therapy can bring better prognosis. Methods: This is a retrospective cohort study conducted in Hunan Cancer Hospital between January 2012 and December 2021 in two Portuguese reference centers. Patients with mCRC who received at least the 2nd line treatment were eligible. Propensity score (PS) would be calculated to balance the baseline characteristics of two arms. Overall survival (OS) was set as the primary endpoint. Results: From July 2019 to October 2022, 106 eligible pts in total were enrolled. After the treatment received, 72 and 34 pts were respectively allocated into FP and TB cohort and TB cohort. With a global median follow-up of 14, the crude OS was 19.4% (95% CI: 17.9-NA) mo in FP cohort vs. 11.6 (10.0-17.2) mo in TB cohort. The HR of FP was 0.384 (95% CI: 0.192-0.769, TB as reference). Multivariable Cox regression showed that the adjusted HR was 0.323 (95% CI: 0.149-0.704), which was adjusted with sex, age greater than 65 yr, EGOS-PS, resection of primary lesion, radiotherapy history, location of lesion (left or right), metastases (liver, lung, and bone), and current line (3 or later). With PS, we performed three statistical methods, namely inverse probability weighting, PS matching (the sample size was 49 vs. 29 after matching), and additional adjustment for PS with multivariable cox regression. The HRs of FP were 0.437 (95% CI: 0.200-0.953), 0.446 (95% CI: 0.201-0.990), and 0.339 (95% CI: 0.153-0.746), respectively. Subgroup analysis showed that FP in patients whose in the subgroup (PS > 65 yr) were comparable, with a hazard ratio of 0.231 (95% CI: 0.117-0.753), right-sided resection (0.177, 95% CI: 0.043-0.736), liver metastases (0.291, 95% CI: 0.112-0.756), and current line greater than 3 (0.303, 95% CI: 0.113-0.812). Additionally in the raw set, the ORR was 16.67% vs. 8.82% (ORFP=2.067, 95% CI: 0.62-2.92). Conclusion: Demonstration of FP demonstrated robustly lower HRs for OS in both crude and PS analysis. Likewise, FP showed better OS and DCR in pts with late-line mCRC than TB, which suggested FP might be a better therapy in late-line mCRC treatment. Research Sponsor: The study was supported by the Changsha Municipal Natural Science Foundation (No. Kq20190178).
Nivolumab in patients (pts) with advanced gastrointestinal (GI) cancers with high plasma tumor mutational burden (pTMB): Results from a SCRUM-Japan G0311A phase II trial. First Author: Yoshikatsu Nakamura, Department of Gastroenterological and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

**Background:** TMB is a biomarker for immune checkpoint inhibitors (ICIs). Analysis of circulating tumor DNA (ctDNA) has the potential to non-invasively identify pts likely to benefit from ICIs by assessing TMB. We conducted a phase II basket trial as part of the SCRUM-Japan G0311A umbrella/basket trial to evaluate the efficacy and safety of nivolumab monotherapy in pts with advanced GI cancers with high pTMB.

**Methods:** Eligibility criteria included histologically confirmed unresectable or recurrent GI cancers; ECOD PS of 0 or 1; refractory or intolerant to the standard therapies; and high pTMB identified by Guardant360 CDx, a 74-gene ctDNA assay. Pts received intravenous nivolumab monotherapy of 360 mg every 3 weeks until progressive disease. The primary endpoint was objective response rate (ORR) for investigator assessment with confirmation. The pTMB score was calculated by adjustment of mutation count by tumor fraction, and initial pTMB thresholds were determined based on previously reported ORR for ICI treatment for each GI cancer in the cohort. The cohort 2 proceeded only for esophageal cancer, and an ultra-high TMB cohort was created to include pts in the top 2% for pTMB scores.

**Results:** Fifty-one pts with high pTMB in the cohort 1/2 (n=32) and the ultra-high TMB cohort (n=19) were enrolled. The median duration of follow-up was 7.5 months (range, 0.9–5.1). Deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) was observed in 1 pt in cohort 1/2 and 2 in ultra-high TMB cohort. The ORR was 12.5% and 21.1%, with median duration of response of 14.0 months and not reached, respectively. In an exploratory analysis of the overall population, pts with esophageal cancer had the highest ORR of 33.3% (4/12), followed by pancreatic (1/6, 16.7%) and colorectal cancer (3/27, 11.1%). Of 2 pts with proficient MMR/non-MSI-H colorectal cancer who had a response, 1 had a POLE mutation. Pts with response tended to have higher pTMB score (median, 26 vs. 8). dMMR/MSI-H (HR=0.16; 95% CI, 0.02–6.14) were significantly associated with longer progression-free survival. Treatment-related grade 3–4 adverse events occurred in 3 pts (9%) in the cohort 1/2 and 3 (16%) in the ultra-high TMB cohort, with no treatment death in either cohort. Conclusions: Nivolumab was well tolerated in pretreated pts with advanced GI cancer and high pTMB. These results suggest that the use of pTMB potentially identify pts who may benefit from ICI treatment. Clinical trial information: UMIN000033182. Research Sponsor: None.

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FOLOFOXIRI ß molecular targeting agent (bevacizumab or panitumumab) for conversion from unresectable to resectable in the advanced/recurrent colorectal cancer (ARC), the introduction of doublet chemotherapy, represented by FOLOFOX/FOLFIRI, and molecular-targeting agents, such as anti-VEGF antibody and anti-EGFR antibody, has given ARC patients a more than three years’ survival. Triplet chemotherapy, such as FOLOFOXIRI ß Bevacizumab or Panitumumab, has already been used in daily practice. These regimens with powerful anti-tumor effects have enabled conversion from unresectable to resectable, giving patients a longer survival than those without conversion. Therefore, we explored the ideal regimen for conversion, focusing on FOLOFOXIRI ß X. **Methods:** We retrospectively reviewed unresectable ARC patients treated with FOLOFOXIRI ß X (X=Smab; n=24, Pmb; n=1, alone; n=2), between February 2015 and December 2022. The results were compared to those of patients who received other regimens (OTHERS; n=212). Results: The median overall survival (OS) was 1072 days. Forty-nine patients acquired conversion. The patients with conversion had a longer progression-free survival and OS than those without conversion (p<0.0001 and <0.0001, respectively). Conversion rates were 57.0% in FOLOFOXIRI ß X vs. 18.4% in OTHERS (p=0.0238), while response rates were 59.3% in FOLOFOXIRI ß X vs. 35.8% in OTHERS (p=0.0185). The RAS wild-type group conversion rates were 30.0% in FOLOFOXIRI ß X vs. 20.6% in OTHERS, while 50.0% in FOLOFOXIRI ß X vs. 15.3% in OTHERS in RAS mutant group. Anti-EGFR antibody ßOHP-based doublet chemotherapy accounted for conversion in 35.3% of the RAS wild-type group. Anti-VEGF antibody ßL- OHp-based doublet chemotherapy was used in 14.3% of the RAS wild-type group. Molecular targeting agent ß doublet or triplet regimens were essential for conversion. FOLOFOXIRI ß X achieved a 88.9% disease control rate, with palliation of symptoms due to a high tumor burden in 10 out of 13 cases. **Conclusions:** Based on these results, FOLOFOXIRI ß X may be an ideal candidate for achieving conversion in first-line treatment of unresectable ARC. Research Sponsor: None.

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A phase I clinical trial of riluzole in combination with mFOLFOX6 and bevacizumab in treating patients with metastatic colorectal cancer. First Author: Chunjie Li, The Ohio State University Wexner Medical Center, Columbus, OH

**Background:** Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in the US. 5-fluorouracil (5-FU) based chemotherapies in combination with anti-angiogenic agents remain the standard of care in patients with metastatic or heavily pretreated advanced disease. It is essential to develop new treatment strategies in metastatic CRC patients with microsatellite stable disease, in whom immune checkpoint blockade is ineffective. Our preclinical studies showed riluzole, an oral medicine for amyotrophic lateral sclerosis, can increase intratumoral CD8+ T cells and suppress tumor growth in a syngeneic colon cancer mouse model. Riluzole-induced tumor growth inhibition depends on the presence of CD8+ T cells and activation of GAS/STING/IFN signaling.

**Methods:** This was a single-arm phase I trial of riluzole in combination with mFOLFOX6/bevacizumab for metastatic CRC patients. The dose of riluzole started from 50 mg twice daily with dose escalation to 100 mg twice daily or dose de-escalation to 50 mg once daily. Patients received riluzole for 16 weeks in combination with mFOLFOX6/bevacizumab for 8 cycles. Then patients either continued mFOLFOX/bevacizumab or switched therapy. The primary objective was adverse events (AE). The secondary objectives were objective response rate (ORR), disease control rate (DCR), and duration of response (DoR). **Results:** Fourteen patients were enrolled, and twelve patients were evaluable. All patients received FOLFOX6 in the past; two patients received 2 lines of chemotherapies; one patient received 3 lines and eight patients had ≥ 4 lines before the study. Five patients (41.7%) had disease resistance to FOLFOX. During the study, two patients received only 2 cycles of treatment due to poor PS. Two patients received 7 cycles, and nine patients completed 8 cycles of treatment. The common grade 3 & 4 AEs included neutropenia (46.2%), lymphopenia (30.8%), and abdominal pain (15.4%). No complete response was observed; two patients obtained partial response; nine patients had stable disease, and only one patient had progressive disease. The ORR was 16.7% and DCR was 91.7%. The median DoR was 5.1 (95% CI 3.2–7.0) months. The maximum tolerated dose for riluzole is 100 mg twice daily. **Conclusions:** Our study showed that riluzole plus mFOLFOX6/bevacizumab is well tolerated in metastatic CRC and may have clinical activity in patients whose disease is resistant to FOLFOX. Further study is necessary to confirm the immunomodulation effect of riluzole. Clinical trial information: NCT04761614. Research Sponsor: The Ohio State University.
Real-world analysis of irinotecan (ir) with or without fluorouracil (5FU) in the second line treatment (2L) of metastatic colorectal cancer (mCRC). First Author: Robert William Lentz, University of Colorado Cancer Center.

**Background:** The most used 1st line (1L) chemotherapy backbone for mCRC is fluoropyrimidine (FP) + oxaliplatin. In the 2L, ir with or alone with 5FU (FOLFIRI), is a biologic agent (biologic), are options. It is unclear whether adding 5FU to ir is beneficial following disease progression on prior FP. **Methods:** This study used the nationwide Flatiron Health electronic health record (EHR) to create the largest database to identify patients diagnosed with mCRC and treated from 01-01-2013 to 02-13-2023 who received 1L+ with FP + oxaliplatin + biological 2L with irinotecan + 5FU: biologic. Baseline patient/tumor characteristics were obtained. The number of major comorbidities was computed using ICD-9-CM/10 codes within 1 year prior to 2L (Quan, 2005). Time to next treatment (TTNT) was defined from the start of 2L to the start of next line treatment (excluding maintenance). For survival outcomes, the median survival time and 95% confidence interval (CI) were estimated using the Kaplan-Meier method. Univariate and multi-variable analyses (UVA and MVA) were performed with the cox proportional hazard model. All covariates were evaluated in UVA, and those significant were included in MVA with adjusted hazard ratio (HR) and 95% CI. Results: 3,215 patients met criteria; most previously received a biologic with 1L (70.5% prior anti-angiogenesis and 5.9% prior anti-EGFR) and had 0 structured major comorbidity diagnoses (82.1%). In the 2L, FOLFIRI was the most used chemotherapy backbone (90.6%, vs in 9.4%), 79% of patients also received a biologic, and who received FOLFIRI were younger (median age 61 vs 65 years) and had better ECOG performance status (87.8% vs 81.8% ECOG 0). OS and survival (OS) was longer with FOLFIRI than ir in (median 14.4 vs 9 months, p < 0.001), as was TTNT (median 7.6 vs 5.3 months, p < 0.001). In MVA, when controlling for age, comorbidities, CEA, ECOG performance status, and 1L, ir was associated with shorter OS than FOLFIRI (HR 1.38, 95% CI 1.21–1.57, p < 0.001). In MVA, the addition of a biologic to FOLFIRI and ir prolonged OS and TTNT in some subgroups (Table). **Conclusions:** In this retrospective real-world analysis of 3,215 patients with mCRC who received 1L with FP + oxaliplatin + biologic, 2L FOLFIRI was associated with longer OS compared to irin alone (both = biologic). Research Sponsor: NIH.

**Poster Session**

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A retrospective analysis of the prognostic impact of KRAS G12D mutation in patients with RAS-mutated metastatic colorectal cancer (mCRC). First Author: Toshiharu Hirose, National Cancer Center Hospital, Chuo City, Japan.

**Background:** KRAS is an oncogene that is mutated in about half of all metastatic colorectal cancers (mCRC). Recently, a novel therapy targeting KRAS G12C mutation has demonstrated promising efficacy for advanced solid tumors, including mCRC. A therapy targeting KRAS G12D mutation is also under development and promising efficacy is expected. However, the prognostic impact of the KRAS G12D mutation in patients with mCRC is still unclear. Methods: We retrospectively reviewed the medical records of patients with mCRC harboring RAS mutation who received first-line chemotherapy between January 2013 and December 2022 at our hospital in Japan. We compared the survival outcomes between patients with KRAS G12D mutation (G12D group) and those with non-KRAS G12D mutations (non-G12D group) in terms of progression-free survival (PFS) and overall survival (OS), using the Kaplan–Meier method and the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated by univariate and multivariate Cox regression analysis. Results: A total of 340 patients were included in this study. The main RAS mutations were KRAS G12D in 80 patients (23.4%), KRAS G12V in 72 (21.2%), KRAS G13D in 43 (12.6%) and KRAS G12C in 16 (4.7%). There were 80 patients in the G12D group and 260 in the non-G12D group. Patient backgrounds did not differ significantly in terms of age (median 61/63), sex (male 49%/48%), performance status (PSO 32%/22%), site of primary tumor (right 33%/32%), number of metastatic sites (3–8% 28%/23%), treatment regimen (doublet 90%/92%, triplet 3%/4%), or first line bevacizumab (yes 81%/79%). Median PFS was 9.2 months (95% CI: 7.8–12.2) in the G12D group and 11.5 months (95% CI: 9.2–13.3) in the non-G12D group (HR 0.97 [95% CI: 0.73–1.28], p = 0.81). Median OS was 25.8 months (95% CI: 18.8–39.8) vs 39.2 months (95% CI: 28.5–46.1) (HR 0.73 [95% CI: 0.60–1.19], p = 0.32). Second-line treatment was administered in 55 (6%) and 192 (74%) patients in the G12D and non-G12D group, respectively. Conversion surgery was performed in 4 (5%) vs 18 (7%) patients in the G12D and non-G12D group, respectively. Multivariate analysis adjusted for PS, age, sex, site of primary tumor, number of metastatic sites and treatment regimen showed no significant difference between the G12D and non-G12D groups. Conclusions: The KRAS G12D mutation did not show a detrimental prognostic impact on PFS and OS compared to KRAS non-G12D mutations in patients with RAS-mutated mCRC. Research Sponsor: None.
Background: TAPUR is a phase II basket study evaluating anticancer activity of commercially available targeted agents in pts with advanced cancers with specific genetic alterations. Results in a cohort of pts with CRC with BRCA1/2 mut treated with Tala are reported.

Methods: Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts received 1 mg of Tala orally daily until disease progression. Primary endpoint was disease control (DC) per investigator defined as complete or partial response or stable disease of at least 16 weeks (wks) duration (SD16) per RECIST v 1.1. Simon 2-stage design tested the null DC rate of 15% vs. 35% (power = 0.85; 1-β=0.85). If <2 of 10 pts in stage I have DC, 18 more pts are enrolled; otherwise, the cohort is closed. If ≥7 of 28 pts have DC, the null DC rate is rejected. Secondary endpoints were objective response (OR), progression-free survival (PFS), overall survival (OS), and safety.

Results: 10 pts with advanced CRC and BRCA1 mut (n=3), BRCA2 mut (n=5), and both (n=2) were enrolled from February 2020 to June 2021. Germline or somatic status was not reported in 7 of 10 pts; 2 pts had somatic BRCA2 muts and 1 pt had a germline BRCA2 mut. 2 pts had left sided tumors, 2 had right sided, 3 had rectal tumors, and 3 pts had tumors that were site undetermined. All pts were evaluable for efficacy and toxicity. Table summarizes pt demographic and outcomes. No pts experienced DC, median PFS was 8 wks (95% CI, 6 to 8) and median OS was 24 wks (95% CI, 7 to 43). Co-alleles were observed in the following genotypes: Kras (3 pts) and BRAF (2 pts). 2 pts had 3 separate grade 3 adverse events of anemia or fatigue at least possibly related to Tala. Conclusions: Monotherapy Tala did not demonstrate sufficient clinical activity in pts with advanced CRC with BRCA1/2 mut. Other tx could be considered for these pts, including tx offered in clinical trials. Clinical trial information: NCT02693535. Research Sponsor: Pfizer; AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Genentech, Merck, Seagen, Taiho Oncology.

Demographics, baseline characteristics and efficacy outcomes (N=10).

<table>
<thead>
<tr>
<th>Median Age, yrs (Range)</th>
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<tr>
<td>OR rate (95% CI)</td>
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<tr>
<td>Median PFS, wks (95% CI)</td>
<td>24(7, 43)</td>
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</table>

108 Oncologic safety of transverse colon cancer surgery without central vessel ligation. First Author: Kyung-Ha Lee, Department of Surgery, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, South Korea

Background: Transverse colon cancers (TCC) have mixed embryological and molecular characteristics of right and left colon cancers and they are difficult to classified to right or left colon cancer due to the ambiguity of their location. Therefore, there is a lack of research about TCC alone, and it tended to be excluded in previous large clinical trials.

Conclusions: Monotherapy Tala did not demonstrate sufficient clinical activity in pts with advanced CRC with BRCA1/2 mut. Other tx could be considered for these pts, including tx offered in clinical trials. Clinical trial information: NCT02693535. Research Sponsor: Pfizer; AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Genentech, Merck, Seagen, Taiho Oncology.

Comparison of outcomes of surgery for TCC has not been established, and the oncologic benefits of central vessel ligation. Oncologic safety of transverse colon cancer surgery without central vessel ligation.

Methods: The study was a single-center retrospective study of consecutive patients undergoing surgery for transverse colon cancers (TCC) at a tertiary care center between March 2016 and January 2022. One hundred and eighteen patients were enrolled.

Results: The median age was 66.5 years (range, 19-82 years). Of the 118 patients, 69 (58.0%) were men and 49 (42.0%) were women. The median body mass index was 25.0 kg/m² (range, 18.2-42.9 kg/m²). The median American Society of Anesthesiologists score was 2 (range, 1-5). The median tumor size was 7.8 cm (range, 0.6-28 cm). The median number of lymph nodes examined was 25 (range, 0-120 nodes).

The median length of hospitalization was 8 days (range, 3-66 days). The overall mortality rate was 2.5% (3 patients). The overall morbidity rate was 28.0% (33 patients). The most common complications were anastomotic leakage (10 patients), wound infection (9 patients), and bile leak (7 patients).

Conclusions: The oncologic safety of transverse colon cancer surgery without central vessel ligation was comparable to that of the standard surgical approach with central vessel ligation. This finding suggests that central vessel ligation is not always necessary for TCC surgery. Further studies are needed to validate these results in a larger population.
Efficacy and safety of trifluridine/tipiracil in combination with bevacizumab in older and younger patients with refractory metastatic colorectal cancer: A subgroup analysis of the phase 3 SUNLIGHT trial. First Author: Julien Taieb, Université Paris-Dîte, (Paris Descartes), Georges Pompidou European Hospital, SIRIC CARPEM, Paris, France

**Background:** SUNLIGHT, an international, open-label, randomized, phase 3 study comparing trifluridine/tipiracil (FTD/TPI) + bevacizumab (FTD/TPI + bev) to FTD/TPI monotherapy in patients with refractory metastatic colorectal cancer (mCRC), demonstrated a 3.3-month increase in PFS compared with 3.5 months with FTD/TPI monotherapy to 10.8 months with FTD/TPI + bev (HR, 0.61; 95% CI: 0.49–0.77; P < 0.001). This subgroup analysis of SUNLIGHT examined efficacy and safety outcomes by age.

**Methods:** In SUNLIGHT, patients with mCRC with ECOG PS of 0-1 and two prior treatment regimens were randomized to receive FTD/TPI + bev or FTD/TPI monotherapy. A subgroup analysis was performed to evaluate efficacy and safety outcomes in patients aged < 65, 65-74, and ≥ 75 years. Concerning overall survival, hazard ratios for FTD/TPI + bev vs FTD/TPI monotherapy were 0.65 (95% CI: 0.48–0.87), 0.64 (95% CI: 0.43–0.94), and 0.49 (95% CI: 0.27–0.90) in patients aged < 65, 65-74, and ≥ 75 years, respectively. Regardless of age, patients receiving FTD/TPI + bev experienced improved progression-free survival and improved time to worsening of ECOG PS to ≥2. Among FTD/TPI + bev treated patients, frequency of any-cause severe adverse events (AEs) was slightly higher in the 65-74 subgroup (69% (65-74); 80% (65-74); 67% ≥75 years). Frequency of grade 3 and 4 neutropenia was also slightly higher in the 65-74 subgroup (36% (65-74); 42% (65-74); 42% ≥75 years); AE-related discontinuation rates were similar across age subgroups (11% (65-74); 13.2% (65-74), and 16.7% ≥75 years).

**Conclusions:** The results of this subgroup analysis demonstrate the efficacy benefit and tolerability of FTD/TPI + bevacizumab treatment regardless of age in refractory mCRC patients. Clinical trial information: NCT04737187. Research Sponsor: Institut de Recherches Internationales Servier; Taiho Oncology.
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Relationship between fluoropyrimidine (FPD) exposure and outcomes in patients with metastatic colorectal cancer (mCRC) receiving trifluridine/tipiracil (FTD/TPI) with or without bevacizumab (BEV) in the context of the SUNLIGHT trial.  

First Author: Marwan Fakhri, Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA  

Background: Standard first- and second-line chemotherapy regimens for mCRC are FPD-based. In the phase 3 SUNLIGHT trial, the addition of BEV to FTD/TPI significantly improved overall survival (OS) compared with FTD/TPI alone in patients with mCRC who had received no more than two previous chemotherapy regimens. Here, we assessed the clinical impact of FPD-free exposure to FPD on efficacy outcomes among patients treated in SUNLIGHT.  

Methods: In this post-hoc analysis, OS, progression-free survival (PFS), and disease control rate (DCR) were assessed in patients treated with FPD within 2 months of enrolment (<2 months FPD-free exposure) and patients who had not received FPD for >2 months prior to enrolment (>2 months FPD-free exposure). Differences in OS between FTD/TPI + BEV and FTD/TPI alone were assessed in each subgroup. The Kaplan-Meier method and log-rank test were used to compare differences in OS/PFS. DCR was compared using Fisher's exact test. The hazard ratio (HR) for OS was estimated using a Cox proportional hazards model. Results: Of 246 patients randomized to FTD/TPI + BEV, 79 had ≥2 months FPD-free exposure and 167 had <2 months FPD-free exposure. Median OS (95% CI) was 11.8 months (9.4–not estimable) for patients with ≥2 months FPD-free exposure and 10.5 months (8.6–11.3) for patients with <2 months FPD-free exposure (P=0.099). Median PFS was 6.7 months (4.6–7.5) and 5.2 months (4.2–5.7), respectively (P=0.043). The DCR among patients treated with FTD/TPI + BEV was 78.9% for patients with ≥2 months FPD-free exposure and 64.7% for patients with <2 months FPD-free exposure, with a between-difference group of 15.1% (95% CI: 3.6%–26.5%; P=0.018). Of 246 patients randomized to FTD/TPI alone, 91 had ≥2 months FPD-free exposure and 155 had <2 months FPD-free exposure. Median OS (95% CI) was 6.7 months (6.0–7.9) and 6.0 months (6.0–7.8) for patients with ≥2 and <2 months FPD-free exposure, respectively (P=0.106) and median PFS was 3.6 months (2.1–3.9) and 2.1 months (2.0–2.7) (P=0.002). The between-difference group in the DCR was 13.8% (50.6% vs. 36.7% for ≥2 and <2 months FPD-free exposure; 95% CI: 20.3%–26.6%; P=0.044). Compared with FTD/TPI alone, FTD/TPI + BEV resulted in longer OS in both the ≥2-month (HR 0.61, 95% CI: 0.41–0.93) and <2-month (HR 0.59, 95% CI: 0.45–0.78) groups, respectively. Conclusions: Owing to imbalances between the ≥2- and <2-month FPD-free exposure groups, the data need to be interpreted with caution. However, with both FTD/TPI + BEV and FTD/TPI alone, OS, PFS, and DCR were numerically higher in patients with ≥2 months FPD-free exposure than in those with <2 months FPD-free exposure, potentially reflecting the better prognosis of the former group. The survival benefits of adding BEV to FTD/TPI were maintained regardless of the timing of exposure to FPD prior to enrolment. Clinical trial information: NCT04737187. Research Sponsor: Taiho Oncology, Inc.  

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Prognostic factors of patients (pts) with salvage-line metastatic colorectal cancer (mCRC). First Author: Hideaki Bando, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan  

Background: Randomized clinical trials provide the best evidence for the effects of a new treatment. However, the use of a placebo control arm may present practical and ethical concerns for enrolled patients and treating providers. The CRC ARCAD global database includes a total of 1,573 individual patient data (IPD) treated with salvage-line chemotherapy for refractory mCRC. By using placebo IPD, we have proposed to construct a synthetic control arm for clinical trials (Yoshida T. et al., Nature Medicine 2023).  

Methods: From 40,899 IPD from 90 studies in ARCAD mCRC database, 723 placebo pts were selected from 4 placebo-controlled randomized studies in a salvage-line setting (CORRECT, RECURVE, CONCUR and TERRA). We analyzed the impact of baseline patient characteristics and various prognostic factors on outcome in the placebo control. Results: The adjusted hazard ratios (HRs) (95% confidence interval[CI]) were 0.52 (0.40–0.67) for the number of metastatic sites (1 vs 2), 0.94 (0.86–1.04) for ECOG performance status (PS) (0 vs 1), 0.54 (0.45–0.66) for liver metastases (No vs Yes), 0.54 (0.40–0.71) for peritoneal metastases (No vs Yes), and 0.51 (0.38–0.70) for Royal Marsden Hospital (RMH) Score (consisting of albumin level, number of metastatic sites, and ECOG PS) (0 vs 1–2–3). Conclusions: Number of metastatic sites, ECOG PS, liver metastasis, peritoneal metastasis and RMH Score were significant prognostic factors in pts with mCRC receiving placebo in a salvage-line setting. Further prognostic factors should be investigated to increase the accuracy of the proposed synthetic control arm. Research Sponsor: ARCAD foundation.  

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Poster Session  

Quality-adjusted time without symptoms or disease or toxicity (Q-TWIST) analysis of fruzurginib + best supportive care (BSC) compared with placebo + BSC in metastatic colorectal cancer (mCRC): Results from the FRESCO-2 trial. First Author: Sebastian Dintzing, Department of Hematology, Oncology and Cancer Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany  

Background: As mCRC and its treatment can adversely impact quality of life (QoL), maintaining QoL is an important treatment goal in addition to improving survival. As mCRC and its treatment can adversely impact quality of life (QoL), maintaining QoL is an important treatment goal in addition to improving survival. There is an unmet need to have an effective systemic immunotherapeutic option for patients with mismatch repair proficient/microsatellite stable (pMMR/MSS) colorectal cancer. The neoadjuvant platform presents an ideal setting as a window of opportunity to evaluate new drugs. The NEST-1 trial explored the safety and efficacy of neoadjuvant botensilumib (BOT), an FC-enhanced next-generation anti-CTLA-4 antibody, alongside balbalitumab (BAL), an anti-FO-1 antibody in patients with colon and rectal cancer who were candidates for surgery. NEST-1 was the first randomized clinical testing the feasibility, safety, and efficacy of the BOT/BAL regimen in neoadjuvant settings for patients with colorectal cancer before resection. All patients received 1 fixed dose of 75 mg of BOT and 2 fixed doses of 240 mg of BAL 2 weeks apart. Patients could proceed to surgery 1 week after completion of the 2nd dose of BAL. Less than 25% of patients were allocated to be mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H). Other inclusion and exclusion criteria were in accordance with ongoing immunotherapy-based clinical trials. Results: The study met its primary endpoints. A total of 12 patients with colon and rectal cancers were safely treated with the BOT/BAL combination without delaying surgery or increasing the risk of any severe adverse events. Significant regression of tumors was noted (Table). Spatial biology analyses on pre-treatment biopsy and post-treatment resection biopsy were performed to assess spatial biology patterns of response/regression; most of the viable tumor if present was superficially oriented. All patients received 1 fixed dose of 75 mg of BOT and 2 fixed doses of 240 mg of BAL 2 weeks apart. Patients could proceed to surgery 1 week after completion of the 2nd dose of BAL. Less than 25% of patients were allocated to be mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H). Other inclusion and exclusion criteria were in accordance with ongoing immunotherapy-based clinical trials. Results: The study met its primary endpoints. A total of 12 patients with colon and rectal cancers were safely treated with the BOT/BAL combination without delaying surgery or increasing the risk of any severe adverse events. Significant regression of tumors was noted (Table). Spatial biology analyses on pre-treatment biopsy and post-treatment resection biopsy were performed to assess spatial biology patterns of response/regression; most of the viable tumor if present was superficially oriented.
First report of the randomized phase III study of bi-weekly trifluridine/tipiracil (FTD/TPI) plus bevacizumab (BEV) vs. FTD/TPI monotherapy for chemorefractory metastatic colorectal cancer (mCRC): JCOG1806 (ROBIT). First Author: Hironaga Satake, Department of Medical Oncology, Kochi Medical School, Nankoku-City, Japan

Background: FTD/TPI has been widely used as one of the standard therapies in the late-line treatment for patients with mCRC, and the efficacy of FTD/TPI plus BEV combination was also recently reported in the SUNLIGHT trial. However, the combination of FTD/TPI plus BEV increased the frequency of hematologic toxicity. On the other hand, several phase II studies suggested that modifying the FTD/TPI schedule in combination with BEV from 4-week intervals (2 weeks-on, 2 weeks-off) to bi-weekly dosing (1 week-on, 1 week-off) reduced hematologic toxicities without reducing efficacy. Therefore, we commenced a phase III study to confirm the superiority of bi-weekly FTD/TPI plus BEV to 4-week intervals FTD/TPI mono-therapy.

Methods: This is a study an open-label, multicenter, phase III trial conducted in Colorectal Cancer Study Group of Japan Clinical Oncology Group. We randomly assigned, in a 1:1 ratio, patients who were refractory or intolerant to fluoropyrimidines, oxaliplatin, irinotecan, and anti-EGFR antibody (if RAS wild type), FTD/TPI, and anti-EGFR antibody (if BRAF v600-mutant), and immune check point inhibitor (if dMMR/MSI-H) to the treatment of mCRC to receive 4-week intervals FTD/TPI 70mg/m²/day monotherapy (arm A) or bi-weekly FTD/TPI plus bevacizumab 5mg/kg (arm B). The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), response rate (RR), disease control rate (DCR), and safety. Results: In consideration of the results of the SUNLIGHT trial, this study was prematurely terminated. Between January 2022 and February 2023, a total of 152 patients were randomized (75 in the arm A and 77 in the arm B). Patient backgrounds between the two arms were well balanced. At the data cut-off date, all enrolled patients discontinued protocol treatment due to disease progression (69.3% vs. 59.7%) and treatment-related adverse events (6.7% vs. 2.6%). With a median follow-up of 8 months for surviving patients (OS events, 45% vs. 40%), the median OS was 12.2 vs. 11.8 months (hazard ratio [HR], 0.905; 95% confidence interval [CI], 0.556 to 1.473) and the median PFS was 2.4 vs. 4.0 months (HR, 0.607; 95% CI, 0.426 to 0.865). RR was 1.3% vs. 5.3% and DCR was 45.3% vs. 53.3%. The most common Grade 3 or higher adverse events in each group were neutropenia (4.0% vs. 5.3%), anemia (15.1% vs. 4.0%), fatigue (2.7% vs. 8.0%), anorexia (5.5% vs. 5.3%), nausea (5.3% vs. 2.7%), and febrile neutropenia (4.1% vs. 0%). Although this trial was terminated early, the bi-weekly FTD/TPI plus BEV combination in late-line chemotherapy for patients with mCRC resulted in prolonged PFS and reduced hematologic toxicity compared to 4-week intervals FTD/TPI mono-therapy. Long-term results including OS, PFS, and OS are expected. Conclusions: Although this study was terminated early, the bi-weekly FTD/TPI plus BEV combination in late-line chemotherapy for patients with mCRC resulted in prolonged PFS and reduced hematologic toxicity compared to 4-week intervals FTD/TPI mono-therapy. Long-term results including OS, PFS, and OS are expected.

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Trifluridine/tipiracil (TAS-102) in combination with anti-EGFR re-challenge versus TAS-102 plus anti-VEGF in patients with mCRC who experienced first-line anti-EGFR-based chemotherapy. First Author: Ching Tso Chen, Department of Oncology, National Taiwan University Hospital Hsinchu Branch, Hsinchu, Taiwan

Background: TAS-102 is one of the standard treatments for refractory metastatic colorectal cancer (mCRC). Add-on bevacizumab to TAS-102 has been proved to improve progression-free survival (PFS) and overall survival (OS). However, the two strategies of combination with anti-EGFR or anti-VEGF or anti-RAS/Raf wild type mCRC patients have not been compared. Methods: We retrospectively collected mCRC patients who received TAS-102 treatment from December 2018 to March 2023 at National Taiwan University Hospital. The key inclusion criteria included RAS/Raf wild type, first-line treatment with anti-EGFR therapy, and TAS-102 in combination with anti-EGFR re-challenge, or with anti-VEGF therapy. Concurrent use of other chemotherapies was allowed. The patients with combination duration less than 4 weeks were excluded. Results: A total of 30 patients were enrolled. There were 20 patients who received TAS-102 plus anti-EGFR re-challenge, and 10 were treated with TAS-102 plus anti-VEGF. The median treatment line of TAS-102 combined with targeted therapies was 5 (Range 3-11). There was no significant difference in baseline characteristics between the two groups (Table). For TAS-102 plus anti-EGFR vs VEGF, the ORR was 30.0% vs 0%, and the DCR was 70.0% vs 30.0%, respectively. The median PFS was 4.0 vs 2.3 (p=0.389) months, respectively. The median OS was 12.6 vs 9.3 (p=0.722) months, respectively. Conclusions: TAS-102 plus anti-EGFR re-challenge showed a higher ORR than TAS-102 plus anti-VEGF. The PFS and OS were comparable in both arm and numerically longer in the TAS-102 plus anti-EGFR re-challenge group. Research Sponsor: National Taiwan University Hospital Hsinchu Branch, Ministry of Health and Welfare (Taiwan).

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Initial efficacy evaluation of fruquintinib plus capcitabine versus capeci-tabine as maintenance treatment for metastatic colorectal cancer (mCRC): A phase II, randomized, controlled, phase IIb/I study. First Author: Wenhua Li, Department of Gastrointestinal Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The standard first-line therapy followed by maintenance treatment is an option to approach the efficacy and toxicity for mCRC. Fruquintinib (Fru), a highly specific inhibitor of VEGFR1/2/3, has demonstrated favorable safety and efficacy outcomes in the treatment of mCRC. In this study, we present findings from an investigation into the comparative efficacy and safety of Fru in combination with capcitabine (Cap) versus Cap as a maintenance therapy for patients (pts) with mCRC.

Methods: Pts with histologically confirmed mCRC who achieved disease control (including CR/PR and SD) after at least six cycles of first-line standard chemotherapy were included in the study. During phase IIb, pts received Fru (4 mg. p.o. q3, weeks on/1 week off, q4w) plus Cap (50 mg/m², p.o. bid, d1-7 and d15-21). In phase II, pts were randomized in a 1:1 ratio to receive either Fru (RPD2, 3mg. 3 weeks on/1 week off) plus Cap or Cap alone. The primary outcome was progression-free survival (PFS).

Results: By Sep 10, 2023, a total of 34 pts were enrolled in the study, and 26 pts were considered evaluable for efficacy. During Fru plus Cap (n=14) and Cap (n=12), the median age was 61.5 (39-78) and 57.3 (25-75) years. The main primary tumor side was left (64.3%/ 66.7%) and approximately half of the pts harbored a RAS mutation (50.0%/ 58.3%). Most pts had previously received bevacizumab (75.0%/ 58.3%) or cetuximab (35.7%/ 25.0%), respectively. The mPFS was significantly improved in Fru plus Cap vs Cap (3.8 vs 3 months, HR 0.629, 95% CI 0.031 to 0.1, p=0.0039). Consistently, ORR (21.4% vs 4%) and DDR (92.9% vs 66.7%) were improved with Fru plus Cap. Grades 3 and 4 treatment-emergent adverse events (TEAEs) were hypertension (11.1%), oral mucositis (5.6%), voice alteration (5.6%), small intestinal obstruction (5.6%), acraddrin (5.6%) and blood bilirubin increased (5.6%) in Fru plus Cap, and anemia (3.6%), oral mucositis (3.6%), and hypocalcemia (3.6%) in Cap therapy. Conclusions: The findings suggest that Fruquintinib Plus Capcitabine can be considered as a first-line maintenance therapy for metastatic colorectal cancer, as it demonstrated a promising improvement in mPFS by 5.3 months while maintaining a controlled level of safety. This study demonstrated a promising improvement in mPFS by 5.3 months while maintaining a controlled level of safety. This study demonstrated a promising improvement in mPFS by 5.3 months while maintaining a controlled level of safety. This study demonstrated a promising improvement in mPFS by 5.3 months while maintaining a controlled level of safety. This study demonstrated a promising improvement in mPFS by 5.3 months while maintaining a controlled level of safety.
Regorafenib plus FOLFIRI with dose-escalated irinotecan according to UGT1A1 genotyping in patients with metastatic colorectal cancer. First Author: Chao-Yuan Wang. Division of Colorectal Surgery, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

Background: This multicenter, phase II, randomized, open-label, 2-arm parallel trial aimed to determine the efficacy and safety profiles of regorafenib plus dose-escalated FOLFIRI according to UGT1A1 genotyping with regorafenib alone in previously treated patients with metastatic colorectal cancer (mCRC). Methods: A total of 153 patients were planned to randomize at a ratio of 2:1 for receiving regorafenib plus FOLFIRI (arm A, 102 patients) or regorafenib alone (arm B, 52 patients), respectively. For both arms, regorafenib were given for 21 consecutive days (Day 1 to 21) of each 28-day cycle at a maintained dose of 120 mg. However, for arm A, patients received regorafenib plus FOLFIRI with dose-escalated irinotecan according to UGT1A1 genotypes. FOLFIRI were on the first day of each 28-day cycle only. The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS) and disease control rate (DCR), and adverse events (AEs). Results: Finally, a total of 116 patients were enrolled to be analyzed, including 74 in arm A and 42 in arm B. The significantly better PFS was observed in arm A, 4.8 and 3.0 months, respectively (p = 0.016). Moreover, in patients with RAS wild type, the significantly better PFS was observed in arm A, 6.9 and 2.5 months, respectively (p = 0.003). The OS was not significantly different between group A and B, 12.6 and 12.5 months, respectively (p = 0.570). However, in patients with RAS wild type, the trend of better OS was observed in arm A, 14.3 and 6.9 months, respectively (p = 0.158). The marginaly significant better DCR was observed in arm A, 55.4% and 38.1%, respectively (p = 0.055). The marginaly significant better DCR was observed in arm A, 55.4% and 38.1%, respectively (p = 0.055). Combination treatment of regorafenib plus FOLFIRI was independent favorable prognostic factor for PFS (p = 0.008; hazard ratio [HR], 1.892; 95% CI, 1.182 – 3.072). Regarding severe AEs, there were no significant differences between the two groups (all P > 0.05).

Conclusions: Combination treatment of regorafenib plus FOLFIRI with dose-escalated irinotecan according to UGT1A1 genotyping results in a significant better PFS and comparable AEs. Moreover, patients with RAS wild type of CRC would be more beneficial for this combination treatment. Research Sponsor: Bayer.
Preliminary efficacy and safety of fruquintinib as maintenance therapy after first-line treatment in metastatic colorectal cancer (mCRC): A multicenter, randomized, open-label clinical trial (the FRONT study). First Author: Xueqiong Xu, Department of Oncology, Cancer center, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Maintenance therapy and discontinuation of treatment are options to mCRC patients who respond to first-line treatment. We conducted this study to evaluate the efficacy and safety of fruquintinib as maintenance therapy after first-line treatment for mCRC.

Methods: This is an ongoing, multicenter, open-label, randomized clinical trial. Patients (pts) with unresectable right-sided mCRC or RAS mutant left-sided mCRC, who hadn’t suffer disease progression after first-line standard treatment (chemotherapy with or without bevacizumab) for four to six months, were eligible. According to the protocol, 110 patients would be randomly assigned (2:1) to fruquintinib (FQ) group (4mg once daily for 21 days, followed by 7 days off in 28 day cycles) or observation (O) group via interactive web response system. The primary endpoint was progression-free survival (PFS).

Results: Up to Aug 22, 2023, 28 and 14 patients had been enrolled in FR group and O group, of whom the median age was 61 (44 to 73) vs. 66.5 (36 to 81), including 20 (71%) vs. 10 (71%) males, respectively. 26% (93%) of 11 (79%) patients were RAS-mutant. In the full analysis set (FAS), the median PFS were 5.26% (95% CI: 3.71-19.12) months and 2.99% (95% CI: 1.91-4.63) months (HR=0.36; p=0.0158), 25 and 13 pts from two groups received at least one response evaluation after baseline, respectively. The disease control rate (DCR) was 88.00% (22/25) vs. 53.85% (7/13) (OR=6.29, 95% CI: 1.31-36.7; p=0.0267). As to the per-protocol set (PPS), since 6 pts in FR group initiated earlier a dose lowning (3mg), the number of patients was 22 vs. 14. The median PFS were 6.51% (95% CI: 3.89-19.12) months and 2.99% (95% CI: 1.91-4.63) months (HR=0.25; p=0.0061). The DCR was 89.47% (17/19) vs. 53.85% (7/13) (OR=7.29, 95% CI: 1.32-82.8; p=0.0331). The common AEs in FR group were hyper-tension, hand-foot syndrome, fatigue, rash, oral mucositis, and proteinuria, while AEs of grade ≥3 were hand-foot syndrome, hypertension, oral mucositis, and proteinuria.

Conclusions: Fruquintinib at a moderate dose level indicated better outcomes of PFS as a maintenance therapy after first-line therapy with acceptable toxicity for patients with mCRC. Clinical trial information: NCT04296019. Research Sponsor: Chinese Society of Clinical Oncology; Eli Lilly and Company Pharmaceutical/Biotech Company.

A phase 1b study of sotorasib combined with panitumumab as second-line treatment of KRASG12C-mutated colorectal cancer. First Author: Rona Yaeger, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In the CodeBreak101 phase 1b study, sotorasib, a KRASG12C inhibitor, plus panitumumab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, showed acceptable safety and promising efficacy for patients with metastatic colorectal cancer (mCRC) who had exhausted standard-line therapies. In the dose escalation cohort of CodeBreak101, the maximally administered dose of sotorasib was 210 mg/d. The objectives of this phase I study were to determine the safety, tolerability, and clinical efficacy of single-agent sotorasib followed by dose expansion in multiple cohorts. Patients eligible for the 2L sotorasib plus panitumumab expansion in multiple cohorts. Patients eligible for the 2L sotorasib plus panitumumab expansion in multiple cohorts.

Methods: CodeBreak101 (NCT04185883) subprotocol H includes dose escalation and expansion in multiple cohorts. In the dose-escalation cohort, KRASG12C inhibitor naïve patients received sotorasib at doses of 3, 10, and 100 mg/d. In the dose-expansion cohort were KRASG12C inhibitor naïve, sotorasib was continued to be administered dose of 10 mg/d. 5% patients experienced grade 3 or 4 treatment-related adverse events (TRAEs). The DLT was related to the exposure of sotorasib. Zelenirstat is a potent oral small molecule pan-NMT inhibitor. Transcriptional analysis of zelenirstat treated cell lines identified an expression signature that predicts cancers most likely to be responsive to NMT inhibition; high sensitivity scores were seen in colorectal carcinomas and diffuse large B-cell lymphoma. The objectives of this phase I study were to establish the safety, tolerability, and maximum tolerated dose (MTD) of zelenirstat monotherapy in patients (pts) with refractory colorectal cancer. The first 21 evaluable patients, DLT was not observed up to and including the 210 mg/d cohort. Gastrointestinal DLTs were seen in the 280 mg/d cohort, establishing 210 mg/d to be the MTD. In doses up to and including 210 mg/d, gastrointestinal adverse events were the most common, reported in 29% of pts; these were primarily GI 1 or 2 diarrhea, nausea or vomiting. Transient Gr 2 thrombocytopenia was seen in 3 pts. Zelenirstat did not induce neuropathy, alopecia, or prolong QT intervals. Plasma concentrations peaked between 1h and 4h, terminal half-lives were 6.7 to 12 h, and steady state was achieved by day 8. Proton pump inhibitors lowered exposure and were prohibited in the higher dose cohorts. At 100 mg/d and higher, trough plasma concentrations exceeded the levels predicted to be therapeutic. The MTD was 100 mg/d.

Conclusions: This is the first report of safety and efficacy of a 2L cohort evaluating a KRASG12C inhibitor plus an anti-EGFR antibody in KRAS G12C-mutated metastatic colorectal cancer. The toxicities of sotorasib plus panitumumab were consistent with the expected safety profile of the individual agents and with that reported previously for this combination; the OAR was similar to that previously reported in KRAS-mutant colorectal cancer patients. In the 2L expansion cohort, the best response was seen in 5 (30%) of 17 evaluable pts, including 1 patient with advanced refractory colon cancer who received 6 cycles of therapy at 140 mg daily dosing prior to PD. Another colon cancer patient with 5 prior lines of therapy continues 210 mg/d dosing after > 5 cycles of therapy, with non-RECIST criteria reductions of approximately 50% in CEA and tumor volumes. Conclusions: Zelenirstat was well-tolerated on a continuous daily oral schedule at doses as high as 210 mg/d, establishing the MTD to be 210 mg. The absence of severe toxicities, attainment of plasma concentrations highly active in preclinical models, and early evidence of clinical benefit in patients with refractory colorectal cancer warrant further trials. Updated data will be presented. Clinical trial information: NCT04856195. Research Sponsor: Pacylex Pharmaceuticals.
Background: treatment with capicitabine and bevacizumab after capicitabine, oxaliplatin, and bevacizumab therapy in metastatic colorectal cancer (mCRC) is shown to be effective with observation as an acceptable alternative. Metastatic burden might be shared decision-making. The aim of this exploratory analysis is to assess the prognostic and predictive value of number and total volume of metastases in mCRC patients included in the CAIRO3 study. Methods: Patients in the CAIRO3 study with liver and/or lung metastases were included. Every individual liver and lung metastasis was counted and volumes were assessed using deep-learning automatic segmentation software (SAS analytical platform and Philips IntelliSpace). Lymph node metastases were counted manually. Each scan was supervised by a dedicated radiologist. Kaplan-Meier analyses were used to estimate progression-free survival (PFS) and overall survival (OS) using log-rank testing for statistical comparison. Hazard ratios (HR) were estimated using Cox regression models. Results: A total of 156 patients were included with 154 OS events, in which 8198 metastases were identified: 5179 were liver metastases, 2835 lung metastases, and 184 lymph node metastases. Patients had a mean age of 63 years and 67% were male. At randomization, the median number of metastases was 9 and mean total metastatic volume was 116 cm³. Median OS for patients with ≤10 versus >10 metastases was 22.0 months (95% CI: 19.3-25.9) and 14.3 months (95% CI: 11.6-20.9, p-value <0.01), with similar differences for low/high tumor volume. In multivariable analysis number and total volume were independent prognostic markers for PFS and OS, respectively, after adjustment for age, sex, WHO performance score, treatment arm, serum lactate dehydrogenase (LDH) level, site of primary tumor, time to metastases, and treatment response. Benefit of maintenance therapy was most pronounced in patients with ≤10 compared to >10 metastases with a PFS HR of 0.42 (95% CI: 0.26-0.71) and OS HR of 0.52 (95% CI: 0.28-0.96) compared to 0.92 (0.42-1.94) compared to 1.17 (0.66-2.08), demonstrating potential predictive value. Conclusions: Metastatic burden is associated with a poor prognosis in patients with mCRC. Patients with limited metastatic disease (≤10 metastases) benefit from maintenance treatment and this could potentially be a predictive biomarker. Research Sponsor: None.

PFS of metastatic burden.

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<th>Median PFS in months (95% CI)</th>
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Prognostic impact of local recurrence and timing of palliative radiotherapy in patients with unresectable recurrent rectal cancer. First Author: Tomoki Sakakida, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan. Background: The standard treatment for unresectable recurrent rectal cancer (URRC) is chemotherapy (CTx) regardless of local recurrence (LR). Approximately 80% of patients with LR experience LR-related pain, making these patients difficult to treat, especially in the context of the timing of radiotherapy (RT). However, the impact of LR and the appropriate timing of palliative RT on prognosis in patients with URRC remains unclear. Methods: This retrospective study included patients with URRC who had an ECOG Performance Status of 0-2 and received fluoropyrimidines plus oxaliplatin or irinotecan as first-line treatment between September 2006 and December 2020 at a single institution. Patients were divided into two groups: patients with LR (LR+), and patients without LR (LR−). Progression-free survival (PFS), overall survival (OS), and post-progression survival (PFS) after first-line CTx were compared between the two groups. The association between receiving palliative RT for LR-related symptoms until disease progression after first-line CTx and the proportion of patients receiving subsequent second-line CTx was also evaluated in the LR+ group. Multivariate Cox analysis, including variables with p < 0.10 in univariate analyses, was performed for PPS. Results: The LR+ and LR− groups included 49 and 99 patients, respectively. No significant differences in the baseline characteristics were detected between the two groups, except liver metastasis, which occurred less frequently in the LR+ group. OS and PPS were shorter in the LR+ group compared with the LR− group (median OS, 33.4 vs. 48.2 months; hazard ratio [HR], 1.52, p = 0.05; median PPS, 17.2 vs. 23.5 months; HR, 1.77, p = 0.01). PFS was similar between the two groups (median PFS, 13.0 vs. 15.8 months; HR, 1.18, p = 0.39). Fewer patients in the LR+ group received second-line CTx compared with the LR− group (68 vs. 83%, p = 0.06). The proportions of patients with PS ≤ 1 (78 vs. 52%, p = 0.007) and PS deterioration at progression after first-line CTx (59 vs. 27%, p = 0.002) were higher in the LR+ group compared with the LR− group. The most common cause of PS deterioration in the LR+ group was LR-related pain (77%). Among patients with LR, further loss of PS was associated with limited metastatic disease (median metastatic burden below 10) numerically lower in patients who did not receive palliative RT than in patients who did receive palliative RT until disease progression after first-line CTx (75 vs. 54%, p = 0.23). Multivariate analysis revealed that receiving subsequent second-line CTx was an independent predictive factor, and for PPS in LR+ patients adjusted HR, 4.77, p = 0.006. Conclusions: The presence of LR is associated with poor prognosis in URRC, which may be due to worsening PS caused by LR-related symptoms and the lower proportion of subsequent CTx. Thus, palliative RT should be recommended more actively when LR becomes symptomatic. Research Sponsor: None.

Immune checkpoint blockade combined with targeted therapies to provide disease control in mismatch repair-proficient colorectal cancer with peritoneal metastases. First Author: Neal Bhutiani, The University of Texas MD Anderson Cancer Center, Houston, TX. Background: Metastatic colorectal adenocarcinoma (mCRC) with proficient mismatch repair (pMMR) genotype and microsatellite stable (MSI) setting is a rare clinical entity with limited treatment options. Although recent immunotherapy (IO) regimens utilizing a combination of immune checkpoint blockade (ICB) and tyrosine kinase inhibitors (TKIs) that suppress tumor-associated macrophages (TAMs) have shown promise in the extra-hepatic, but not hepatic metastases. However, few studies include patients with peritoneal metastases (PMs) and the response rate of PMs to these therapies is unknown. We sought to examine the disease control rates (DCR) and OS of patients treated with ICB who were treated with ICB regimens. Methods: Patients with pMMR tumors treated with ICB and TKI after progression on first- and second-line therapy from 2015 to 2022 were identified. The primary endpoint is ORR, and secondary endpoints included safety, DCR, DOR and PFS. Results: From November 2019 to February 2021, 30 eligible patients were enrolled, of whom, median age was 60y (range, 32-72y), 26 (86.7%) had left colon or rectal cancer, and 25 (83.3%) had liver metastases. In previous reports, ORR, DCR, and median OS were 76.7%, 92.3%, and 11.3 months, respectively. A median follow-up of 31.7 months (95% CI, 27.9-35.6), the median OS was 29.7 months (95% CI, 21.2-39.2), the 24-month OS rate was 55.0% (95% CI, 35.4-70.9) and the 30-month OS rate was 40.6% (95% CI:21.6-58.9%). Conclusions: Anlotinib combined with oxaliplatin and capicitabine achieved significant OS and showed potential efficacy as first-line therapy for mCRC with manageable toxicity profiles. Clinical trial information: NCT04801043. Research Sponsor: None.
Clinical characterization and therapeutic outcomes of patients (pts) with colorectal cancer (CRC) harboring somatic BRCA1/2 mutations. First Author: Deenesh Bhambhani, The University of Texas MD Anderson Cancer Center

Background: Somatic BRCA1/2 mutations in CRC-associated cancers increase therapeu- tic sensitivity to platinum-based chemotherapies and PARP inhibitors, but the im- plications of BRCA mutations in non-CRC-associated cancers such as CRC is unknown and hypothesized to be shaped by tumor lineage. We thus conducted a retrospective analysis of outcomes with platinum-based chemotherapy and PARP inhibition in pts with CRC, where the estimated prevalence of BRCA2 alteration is 3.4%. Methods: pretreatment blood or tissue next generation sequencing (NGS) positive for a somatic BRCA1/2 variant and a diagnosis of CRC were identified from a single institution database. The patho- genicity of each mutation was annotated using public genomic databases (e.g. ClinVar). Pt characteristics were compared using Fisher's exact or chi square test. To compare survival outcomes, Kaplan-Meier survival analysis with log-rank test was used for comparison of survival distribution among groups. Results: 8,258 NGS reports with a BRCA1/2 alteration from 1,670 CRC pts (18%) were identified of which 119 (11%) had a diagnosis of CRC. 148/189 CRC pts (79%) had ≥1 pathogenic BRCA1/2 variant, 19 pts (10%) had ≥1 benign variant, and 143 pts (69%) had ≥1 variant of unknown significance (VUS); 26 pts (14%) had more than one BRCA1/2 variant. Pts with ≥1 pathogenic mutation (n=84) were more likely to have an inactivating DNA polymerase epsilon (POLε) mutation versus pts with only benign/VUS BRCA1/2 variants (n=135) (20% vs 6%, p=0.004) while prevalence of microsatellite instability (MSI-H) (19% vs 13%, p=0.03) and Ras/Raf (53% vs 53%, p=1.00) were similar between groups. Median progression free survival (PFS) among 115 CRC pts (unselected for BRCA1/2 pathogenicity) who received an oxaliplatin-based regimen for advanced disease in the 1st line (n=82) was similar to the median PFS among pts who received an irinotecan-based regimen (n=63) (7.0 vs 7.0 mths, p=0.48). Median PFS with an oxaliplatin-based regimen in the 1st line among 52 pts with pathogenic BRCA1/2 variant (n=31) was 5.1 mths vs 5.5 mths among pts with wild-type BRCA1/2 variants (n=38) (p=0.39). There were no significant differences in median PFS among pts with a pathogenic vs benign/VUS BRCA1/2 variants when the analysis was restricted to pts with BRCA1/2 variants identified in tissue (p=0.76) and to pts without co-occurring driver mutations (Ras/Raf, MSI-H, and/or POLε) (p=0.1). Overall survival in patients with advanced disease was similar between pts with a pathogenic (n=52) vs non-pathogenic/VUS (n=122) BRCA1/2 variants (37.1 mths vs 45.1 mths, p=0.14). 6 pts (4% with pathogenic BRCA1/2 and 3 with VUS) received a PARP inhibitor after a median of 3 lines of treatment and the best response was disease progression in 6 pts (100%). Conclusions: In the context of CRC, somatic BRCA1/2 mutations frequently co-occur with pathogenic POLɛ mutations, but do not appear to confer therapeutic benefit to platinum-based chemother- apy and PARP inhibitors. Research Sponsor: None.

Amivantamab monotherapy in relapsed/refractory metastatic colorectal cancer: OrigAmI-1, an open-label, phase 1b/2 study. First Author: Gliezer Osterby, NYU Langone Health, New York, NY

Background: Amivantamab (ami), an EGFR-MET bi-specific antibody with immune cell-directing activity, has shown preclinical activity in colorectal cancer (CRC) models. MET amplification is implicated in driving resistance to anti-EGFR therapies in metastatic CRC (mCRC). We hypothesize that dual, co-inhibition of EGFR and MET with ami could improve outcomes in relapsed/ refractory mCRC pts. Methods: OrigAmI-1 (NCT05379955) is assessing the safety and efficacy of ami as monotherapy in pts (n=26) with refractory mCRC in 3 separate cohorts (Table). Eligible pts were wild-type for KRAS, NRAS, BRAF, and EGF R ectodomain by ctDNA testing, without RBEB2/HER2 amplification. Cohorts A and B included pts with left-sided mCRC without/prior ex- perience of anti-EGFR monoclonal antibodies, respectively, and cohort C included pts with right-sided mCRC. Safety population included all pts receiving the recommended phase 2 dose (RP2D; 1050 mg [1400 mg, ~80kg]). Investigator-assessed response per RECIST v1.1 is reported for evaluable pts with post-baseline disease assessment(s) or who discontinued for any reason. Ami plus FOLFOX or FOLFIRI is being explored in additional cohorts. Results: As of September 4, 2023, 93 pts were treated at RP2D; 89 were response evaluable (median follow-up: 4.4 m). Median age was 60 years, 66% were male, and median prior lines of therapy were 2, with 94% receiving prior bevacizumab and 69% prior anti-EGFR therapy. Best response timepoints were: Cohort A: 7/17, 41.2%; Cohort B: 13/54, 24.1%; Cohort C: 1/18, 5.6%. Disease control rate (DCR) were 88.2%, 72.2%, and 77.8% for Cohorts A, B, and C, respectively. Median duration of response (mDoR) for confirmed responders was 7.5 and 7.4 m for Cohorts A and B, respectively. Treatment discontinuing for the responder in Cohort C: 10-13 responders (77%) remain on treatment. Preliminary biomarker data suggest ami may be active in alterations associated with anti-EGFR antibody resistance (eg, EML4-ALK fusion, PTEF). The most frequent treatment-emergent adverse events were rash (84%) and infusion-related reactions (53%). No new safety signals were ob- served. Updated results will be presented at the meeting. Conclusions: Ami monotherapy demonstrated promising, durable antitumor activity in refractory mCRC, including pts treated with prior anti-EGFR therapy and pts with right-sided disease. The safety profile of ami in mCRC is manageable and consistent with prior NSCLC experience. Clinical trial information: NCT05379955.

Efficacy

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*confirmed responders.
† confirmed,_pending confirmation, 1 unconfirmed.
‡ confirmed, pending confirmation, 1 unconfirmed.
§ confirmed.

Conclusion: In confirmed responders.

Real-world data of TAS-102 therapy in refractory metastatic colorectal cancer (mCRC): The experience of the University Hospital of Montreal (CHUM). First Author: Reem El Khouy, Centre Hospitalier de l’Université de Mon- treal (CHUM), Montreal, QC, Canada

Background: Colorectal cancer poses a substantial healthcare burden due to its ele- vated incidence and high mortality rate. Tracing the underlying refractory metastatic cancer causes remains a challenge in our practice due to the paucity of therapeutic options. Treatment with Trifluridine-Tipiracil (TAS-102) prolonged overall survival among patients (pts) with mCRC. This study investigates the efficacy of TAS-102 therapy in this patient population and explores various prognostic factors influencing clinical outcomes. Methods: We retrospectively reviewed the data of 53 patients with refractory mCRC treated with at least 1 cycle of TAS-102 at CHUM between March 2018 and January 2023. Multivariate and univariate analyses were employed to evaluate the impact of age, number of prior treatments, presence of KRAS mutation, gender, tumor origin, and Eastern Cooperative Oncology Group (ECOG) performance status on progression-free survival (PFS) and overall survival (OS). Survival analysis was conducted using the Kaplan-Meier method, and Cox regression analysis assessed prognostic factors. Results: The median age was 61 years (23-82), and 27 pts (50.9%) were females. Twenty-two pts (41.5%) had their primary tumor located in the left colon, 17 pts (32.1%) had right-sided tumors, and 14 pts (26.4%) had rectal tumors. 52% of pts received TAS-102 after 2 lines of therapy and 43% beyond third line. The performance status was: ECOG 0/1 in 46 pts (86.8%), and ECOG 2 in 7 pts (13.2%). In our refractory mCRC pts, median PFS was 3 months and median OS 7 months. Univariate analysis demonstrated no significant differences in PFS or OS based on patient sex, KRAS mutation status, tumor sidedness, or the number of prior treatments. In univariate and multivariate analysis ECOG 0/1 pts compared to ECOG 2 in refractory mCRC (HR = 0.33; p = 0.051 and HR = 0.24; p = 0.0086). Conclusions: In our real-world experience, clinical outcomes were comparable to the findings from the RECURVE trial, suggesting improved PFS and OS with TAS-102 in heavily pre-treated mCRC patients. ECOG performance status remains a significant prognostic factor and underscores its importance in our treatment decisions for this patient population. Research Sponsor: None.
Frugnulinib with PD-1 inhibitors versus frugnulinib monotherapy in late-line mCRC: A retrospective cohort study based on propensity score matching. First Author: Tianqi An, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

Background: Immune checkpoint inhibitors (ICIs) are highly effective in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC). However, the population of MSI-H/dMMR only accounts for 5% of mCRC. And most of the remaining microsatellite stable or proficient mismatch repair (MSI-stable/dMMR) mCRC patients appeared not to benefit from mere immunotherapy. Frugnulinib was the standard third-line regimen for mCRC in a Russian small-scale antiangiogenic tyrosine kinase inhibitor. Studies demonstrated that frugnulinib combined with programmed death receptor-1 (PD-1) inhibitors (FP) can reverse the immunosuppression and achieve promising efficacy. However, due to the lack of research comparing the efficacy between frugnulinib monotherapy (FM) and FP, it remains uncertain whether FP can bring extra benefit. Methods: This was a retrospective cohort study conducted in the First Affiliated Hospital of Zhengzhou University. Patients (pts) with MSI/dMMR mCRC who had received at least the 2nd line treatment were eligible. Propensity score (PS) was calculated to balance the baseline characteristics of two cohorts. Progression-Free survival (PFS) was set as the primary endpoint. The Kaplan–Meier method and Cox proportional hazard model was used to evaluate PFS and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Results: From Apr 2020 to Jan 2023, 83 eligible pts in total were enrolled. According to the treatment received, 47 and 36 pts were respectively allocated into FP cohort and FM cohort. With a global median follow-up of 16.5 mo, the crude PFS of FP is 6.8% (95% CI: 4.3-11.3) vs. 17.1% (95% CI: 10.4-24.8) in FM cohort. The HR of FP was 0.58 (95% CI: 0.34-0.98, FM as reference). Multivariate Cox regression showed that the adjusted HR was 0.49 (95% CI: 0.26-0.93), which was adjusted with sex, age greater than 65 yr, ECOG-PS, RAS, and our data confirm the results of clinical trial, its utilization and use provides only modest clinical

Methods: Patients with advanced malignancy who had failed standard treatment were administered Deflexifol as a bolus followed by a continuous 48-hr infusion. The total dose was escalated across four levels (2400 mg/m2 to 3800 mg/m2) in the absence of dose-limiting Toxicity using a traditional 3+3 design; the bolus dose was fixed at the previously declared MTD of 525 mg/m2. The stated Deflexifol dose represents the dose of standard 5-FU delivered. Primary trial objectives were to determine the safety and tolerability of a bolus plus infusion regimen of Deflexifol, with a secondary objective to determine the pharmacokinetics and MTD. Efficacy was an exploratory objective. Results: Nineteen patients with mainly colorectal (n=13) and breast (n=4) cancers were enrolled and treated with Deflexifol. Approximately two-thirds of patients had previously received fluoropyrimidine treatment. Deflexifol was generally well tolerated, with the MTD declared as a 525 mg/m2 bolus plus 3400 mg/m2 infusion. Treatment-related toxicities were consistent with standard 5-FU/LV therapy; the most frequent Grade 1/2 adverse events were fatigue, mucositis, and diarrhea. Grade ≥3 adverse events were reported in 6/19 patients, including mucositis (2/19) and haematological toxicity (5/19). One treatment-related death occurred at the highest infusion dose level of 3800 mg/m2 due to haematological toxicity. Quantifiable 5-FU and LV concentrations were exhibited at all time-points. Disease control, including one partial response, was achieved in 9/13 evaluable patients. Conclusions: Deflexifol is safe and well tolerated at doses of 5-FU up to 40% higher than typically administered by the standard modified de Grammont regimen. 5-FU and LV exposure extended throughout the entire dosing period, substantially longer than reported for standard treatment. Disease control was achieved in 69% of patients. Clinical trial information: ACTRN12619001533189. Research Sponsor: FivepHusion.

Methods: Real world effectiveness of regorafenib in heavily pretreated patients with metastatic colorectal cancer. First Author: Anastasia Danilova, Moscow City Oncology Hospital 62, Krasnoskryskiy Rayon, Russian Federation

Background: Metastatic colorectal cancer (mCRC) remains a challenge with a significant impact on patient survival and quality of life. Over the past decade, targeted therapies have emerged as promising treatment options for mCRC, including regorafenib. While clinical trials have established efficacy and safety of regorafenib in mCRC, based on the CORRECT and ReDos trials, the real-world utilization and outcomes associated with this therapy have gained increasing importance. This abstract describes a real-world data analysis focused on the use of regorafenib in patients with metastatic colorectal cancer in a community based comprehensive cancer center in Moscow, Russia. The data were collected from 2 outpatient medical oncology departments from 2018-2022 and we evaluate the real world patterns of use. Results: We evaluated all patients who were regorafenib naive at a medical pharmacy of our cancer center. We evaluated all Regorafenib issued from 2018-2022 in our center – 348 patients received Regorafenib and 311 of them were patients with metastatic colorectal cancer and identified patterns of use, toxicity and outcomes in this patient population. Results: The median age was 61.2 and 49.5% were female (50.5 – were male). Primary tumor was right sided in 20.9% of all patients, left sided – 49.1% and rectum in 29.9%. De novo metastatic colorectal cancer was in 208 patients and 103 patients were those who progressed after initial treatment. Mutation status was identified in 91% of all patients. 46% had KRAS mutation, 3.8% were BRAF mutated and 4.2% were NRAS mutated. MSI status was known for 71% of the patients and it was negative. We understand the selection bias, because most of MSI-pTS patients would have gone on to receive immunotherapy rather than a TKI. The patients identified in practice were more heavily pretreated (93.5% of them received more than 3 lines of prior therapy) and 1/3 of all patients were ECOG 2-3 performance status. Toxicity data were available only in 61% of the patients which reveals data caviats when using real world data outside of a clinical trial. Disease control was noted in 53% of all patients. Using Kaplan Myer Survival Analysis, the median PFS was 2 months and median OS was 5.5 months in the evaluated population. Conclusions: The real world data analysis shows that while Regorafenib is another treatment option, and our data confirm the results of clinical trial, its utilization and use provides only modest clinical benefit for patients. Research Sponsor: None.

Methods: Impact of early tumor shrinkage and depth of response in patients with BRAF V600E-mutant metastatic colorectal cancer. First Author: Shohei Udagawa, Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Early tumor shrinkage (ETS) and the depth of response (DpR) are early-onset surrogate markers for survival in patients with metastatic colorectal cancer (mCRC) receiving anti-epidermal growth factor receptor (EGFR) monoclonal antibody. However, the utility of ETS and DpR for BRAF V600E mutant (MT) mCRC which has a poor prognosis remains unclear. The aim of this study is to evaluate the association between ETS and DpR and clinical outcomes in BRAF V600E MT mCRC. Methods: mCRC patients who were diagnosed BRAF V600E MT and treated with 1st line chemotherapy from June 2011 to March 2023 at single cancer institute were enrolled. We analyzed the association between ETS and DpR and clinical outcome in patients who had at least one target lesion. Subgroup analysis of clinical factors related to progression free survival (PFS) and overall survival (OS) was performed using multivariate analysis. ETS was defined as the relative change in the sum of the longest diameters of RECIST target lesions at first follow-up CT scan compared to baseline and DpR was defined as the relative change in the sum of the longest diameters of RECIST target lesions at the nadir in the absence of new lesions or progression of non-target lesions compared to baseline. Results: In total, 54 patients of BRAF V600E MT mCRC had at least one target lesion. In total of Stage-IV CRC patients, the incidence of BRAF V600E MT was 6.3% (235/3705). Patients with ETS ≥ 20% and DpR ≥ 25% (median value) were 24 (44.4%) and 27% (50) respectively. PFS was 7.5 months (95% confidence interval (CI), 5.0-9.9) and OS was 17.1 months (95% CI, 11.7-20.2). Patients with ETS ≥ 20% had longer PFS and tended to have longer OS than those with non-ETS, with a median PFS of 9.6 months vs. 4.3 months (P log-rank = 0.045, hazard ratio (HR), 0.55; 95% CI, 0.30-1.00), and a median OS of 22.6 months vs. 11.6 months (P log-rank = 0.18, HR, 0.67, 95% CI, 0.37-1.21). Patients with DpR ≥ 25% had also longer PFS and OS than those with non-DpR, with a median PFS of 11.0 vs. 4.3 months (P log-rank < 0.01, HR, 0.36; 95% CI, 0.20-0.66) and a median OS of 22.6 vs. 10.1 months (P log-rank = 0.047, HR, 0.55; 95% CI, 0.31-1.00). Median OS of DpR ≥ 30% was 3.6 months (P log-rank = 0.045, HR, 0.55; 95% CI, 0.30-1.00) and was significantly associated with both longer PFS (HR, 0.27, 95% CI: 0.14–0.55, P < 0.01) and OS (HR, 0.52, 95% CI: 0.29–0.96, P = 0.04). Conclusions: ETS and DpR may be early surrogate markers for clinical outcome in BRAF V600E MT mCRC who were treated with 1st line chemotherapy. Research Sponsor: None.
BOLD-100-001 (TR0039): A phase 2 study of BOLD-100 in combination with FOLFOX in patients with advanced mCRC previously treated with FOLFOX/CAPOX—Efficacy and safety analysis. First Author: Jennifer L. Spratlin, Cross Cancer Institute, Edmonton, AB, Canada

Background: BOLD-100 is a first-in-class metallotherapeutic with a unique multimodal mechanism of action currently in phase 2 clinical development for the treatment of advanced gastrointestinal cancers. Standard treatment options for patients (pts) with metastatic colorectal cancer (mCRC) include FOLFOX or CAPOX in first or second line therapy. This study explored the benefit of BOLD-100 + FOLFOX in previously treated mCRC patients. Methods: This prospective, phase 2 study evaluates BOLD-100 + FOLFOX in pts with mCRC. All pts received prior standard treatment, including FOLFOX or CAPOX. Pts received 625 mg/m² of BOLD-100 + FOLFOX on day 1 of each 14-day cycle and treated until progressive disease or unacceptable toxicity. The primary objective is to evaluate PFS, OS, and safety (Response Evaluation Criteria in Solid Tumors [RECIST]) and Disease Control Rate (DCR). Results: As of 31 Aug 2023, 36 pts with advanced mCRC were treated. Median age was 62 years (range 40-78), 56% were women, all pts were EGCG 0 (25%) or 1 (75%). Enrolled pts had a median of 4 prior systemic therapies, including FOLFOX/CAPOX. All but one patient had stage IV disease. On study, pts received a median of 6 cycles of BOLD-100 + FOLFOX [range 1-17]. Five pts remain on treatment with 19 in follow-up. Median PFS was 3.9 [2.7, 5.7] months, median OS 9.6 [6.0, 17] months, ORR 7% [1.01, 2.8] and DCR 76% [58, 88] in the 29 evaluable pts. Two pts achieved a partial response, and 2 pts had target lesion tumor decreases between 20-29%. Study treatment was well tolerated. Of the 36 treated pts, 33 had 1 or more treatment-emergent adverse events (AEs), most common neutropenia (n=17, 47%), nausea (n=12, 42%), fatigue (n=9, 25%) and febrile neutropenia (n=6, 17%). Most related AEs were grade (G) 1-2. 15 pts (42%) had G3/4 neutropenia. Despite previous oxaliplatin treatment, fewer than 6% of pts reported peripheral neuropathy or sensory neuropathy and all were G1/2. Conclusions: BOLD-100 + FOLFOX is an active and well-tolerated treatment in this heavily pre-treated Stage IV mCRC study population. There were no new safety signals. The mPFS, mOS, ORR and DCR data demonstrate significant clinical benefit and improvement over the currently available therapies, with minimal treatment emergent neuropathy or significant toxicities. This promising treatment combination should be further studied. Clinical trial information: NCT04421820. Research Sponsor: Bold Therapeutics Inc.

Induction chemotherapy plus concomitant oxaliplatin-based chemoradiotherapy for locally advanced rectal cancer: A real world experience at San Raffaele Hospital. First Author: Valentina Burgio, Department of Medical Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background: The standard treatment of locally advanced rectal cancer (LARC) consists of giving preoperative chemoradation therapy (CT/RT) followed by surgery. Recently, total neoadjuvant therapy (TNT) has shown greater efficacy in terms of increasing the rate of complete pathological response (pCR) and reducing local and systemic relapse. However, based on the proposed therapy scheme, the risk of overtreatment and side effects is not negligible. The objective of this study was to evaluate the efficacy and safety of neoadjuvant doublet with oxaliplatin-based CT and concomitant RT. Methods: Patients with clinically staged II-III rectal cancer were treated with preoperative CT/RT using up to 3 cycles of oxaliplatin and fluoropyrimidines plus pelvic radiation daily, for a total dose of 46.2 Gy in 18 fractions. The first cycle of mXELOX (oxaliplatin 85 mg/m², D1 start, capecitabine 2525 mg/m², BID) was administrated before RT (as induction CT); the other 2 cycles of mXELOX were administrated concurrent with RT, with capecitabine continued until the end of RT. Radical resection was performed within median 11 weeks of the last dose of RT. Adjuvant CT with FOLFOX or XELOX was administered according to pathological report. Results: Between 2007 and 2022, a total of 186 patients were enrolled, mean age was 61 years. 19 (10.2%) patients were clinically stage II and 167 (89.8%) were clinically stage III. Any grade most common toxicities during neoadjuvant CT/RT included diarrhea (53.2%), proctitis (51.2%) and neutropenia (14.5%). The most common grade 3/4 toxicity was diarrhea (9.1%). A total of 146 (78.5%) patients achieved a downstaging at CT/RT and 174 (95.3%) patients had a downsizing on pathological report. Adjuvant treatment was planned for all patients. Conclusions: Considering the low rate of toxicities and the comparison of outcomes of downsizing, pCR, probability of DFS and OS to other TNT regimens proposed in recent studies, our schedule of neoadjuvant CT/RT may represent a potential alternative to standard CT/RT in selected patients with LARC. Research Sponsor: None.

Natural history and patterns of progression for dMMR/MSI-H colorectal cancer treated with immune checkpoint blockade: A single center retrospective analysis. First Author: Victoria Higbie, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Deficiency in mismatch repair or high microsatellite instability (dMMR/ MSI-H) are each present in approximately 20% of all colorectal cancer (CRC) cases and approximately 4% of metastatic CRC (mCRC), predicts clinical benefit of immune checkpoint blockade (ICB). With response rates of about 50% in mCRC and higher in localized cases, ICB is providing durable benefit and even cure in a meaningful portion of cases. However, further understanding of those patients who progress and treatment options following progression are needed. In this single institution retrospective analysis, we examined the clinical characteristics, treatment and outcomes of locally advanced and metastatic colorectal cancer (CRC) cases who progressed while on treatment with immune checkpoint blockade. Methods: A single institution retrospective review was performed on 151 dMMR/MSI-H CRC patients receiving ICB at MD Anderson Cancer Center from 2014 to 2023. Data was collected including patient demographics, tumor and mutational data, ICB treatment data, progression patterns, and treatment following progression. Progression patterns were classified as intrinsic (progression at initial restaging with pseudoprogression excluded) or adaptive progression and oligometastic (3 or less sites of metastatic disease regardless of organs involved) or systemic progression. Results: The median time to progression (TTP) of all patients treated with ICB was 88 months (M). Median follow up was 40 months. Of the 151 patients, 59 (39%) progressed on ICB. The majority of these were treated with monotherapy anti-PD1 (49, 85%) while only 10 (17%) were treated with combination ICB. Of those that progressed, 29 (49%) were considered intrinsic while 30 (51%) were considered adaptive. In the adaptive group, average TTP was 21 months. The majority progressed at a metastatic site (51, 86%) and at a prior site of disease (47, 80%). Progression was oligometastatic in 30 (51%) patients and systemic in 29 (49%) patients. The median TTP for oligometastatic progression was 9.6 months. The median TTP for systemic progression was 4.4 months (M). The median OS for those with systemic progression was 17 months while the median OS for oligometastatic progression was not reached (p=0.027). Of those with progression, 12 (20%) had no-surgical local therapy to progressing sites, 6 (10%) underwent surgery to progressing sites, and 31 (52%) received alternative systemic therapy (chemotherapy or ICB). Of those that progressed, 10 (17%) underwent local therapy, 7 (12%) had surgery to progressing site, and 24 (41%) remain with no evidence of disease. Conclusions: This is one of the largest reviews of dMMR/MSI-H CRC progressors on ICB. Adaptive progression represented approximately one half of all progression events and local-modality therapy was utilized in 27% of patients. Long-term disease control was seen in oligometastatic adaptive progressors who received local modality therapy. Research Sponsor: None.

The interaction of radiotherapy and dual inhibition of BET and HAT/p300 in colorectal cancer. First Author: Michael Matthew Pennock, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: Colorectal cancer (CRC) is characterized by extensive DNA methylation at promoters of tumor suppressor genes and enhanced activity of histone modifying effects. BET and HAT/p300 are epigenetic enzymes that regulate transcription and are targets of clinical interest. Methods: HCT116 CRC cells. Flow cytometry was used to assess DNA damage (H2A.X), apoptosis (Annexin V–PI assay), cell cycle analysis, and proliferation (EdU). Results: There was a significant dose-dependent increase in the residual DNA damage at 6 hours (80Gy + EP 0.5μM vs. 8Gy, p<0.001) and 24 hours (80Gy + EP 0.5μM vs. 8Gy, p=0.002) for combination therapy over RT alone. Four-hour treatment with EP promoted apoptosis (n=6, 17%) and proliferation (n=8, 22%), fatigue (n=7, 19%) and infusion related reaction (n=7, 19%). Conclusions: Inhibition and viability between the various drug, RT, and combination groups. Synergy between treatments was evaluated by estimating the combination index (CI) values via mass-action law Compudyne calculations using CV data. CI values of <1 from the growth inhibition assay suggested that EP synergized with RT for enhanced cytotoxicity in HCT116 CRC cells. Flow cytometry was used to assess DNA damage (γH2A.X), apoptosis and total death (Annexin V–PI assay), cell cycle analysis, and proliferation (EdU). Results: There was a significant dose-dependent increase in the residual DNA damage at 6 hours (80Gy + EP 0.5μM vs. 8Gy, p<0.001) and 24 hours (80Gy + EP 0.5μM vs. 8Gy, p=0.002) for combination therapy over RT alone. Four-hour treatment with EP promoted G2 cell-cycle arrest (80Gy + EP 0.5μM vs. 8Gy, p<0.001) and significantly reduced the number of HCT cells in S-phase (80Gy + EP 0.5μM vs. 8Gy, p<0.001) and proliferation (EdU) of the HCT cells (80Gy + EP 0.5μM vs. 8Gy, p<0.001) compared to RT alone. There was a significant increase in apoptotic cells the combination group (80Gy + EP 0.5μM vs. EP 0.5μM, p=0.008) when compared to the unirradiated cells. The combination group also showed significant increase in the total death compared to RT alone (80Gy + EP 0.5μM vs. 8Gy, p=0.03) at the GI-1 checkpoint. Conclusions: EP31670 enhanced RT effects in CRC cells, and enhanced cell death in CRC cells in synergy with the RT. Additional preclinical studies, in vivo studies, and clinical studies can be conducted to further exploit this synergistic interaction. Research Sponsor: None.
Results of a prospective phase II study of total neoadjuvant therapy for locally advanced rectal cancer. First Author: Huaying Ma, State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center, National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China

Background: Total neoadjuvant therapy is further accepted for the treatment of locally advanced rectal cancer, which is more valuable for patients with high-risk factors. Optimal schedule of radiotherapy and chemotherapy remains unknown and needs further exploration. Methods: We conducted a multicenter, randomized, phase II trial (ClinicalTrials.gov No.: NCT04543695). Patients aged 18-75 years with initial stage II/III rectal adenocarcinoma (At least one of high-risk factors should be included: mesorectal fascia involvement, T4, N2, positive lateral lymph node, or extramural vessel invasion) were assigned into three groups. 1) Chemoradiotherapy (50 Gy of radiation combined with oral cetuximab) followed by consolidation chemotherapy using six cycles of XELOX(CNCT group), 2) Induction chemotherapy before chemoradiotherapy (INCT group), or 3) Chemoradiotherapy alone (Control group). Then enrolled patients were required to undergo radical surgery after neoadjuvant therapy. Patients in Control group need six cycles of XELOX after surgery. The primary end point was proportion of ypT0-II, and a watch-and-wait strategy after complete clinical response (cCR) was allowed. Results: Of the 257 patients enrolled, 255 patients were evaluable (Control: CNCT: INCT= 84: 86: 85). Neoadjuvant treatment related grade 3 or 4 toxicity was higher in TNT approach (7.1%, 23.3% and 32.9% in Control, CNCT and INCT, respectively). As to CNCT and INCT, 50.9% and 74.1% of patients achieved six cycles of chemotherapy with 76.7% and 83.5% completing four cycles of chemotherapy, respectively. Proportion of downstage (ypT0-II + cCR) were achieved 75.6% in CNCT group and 74.1% in INCT group, respectively, compared to 56.0% in Control group. CR rates (PCR + sustained cCR) were achieved 43.0% in CNCT group and 38.8% in INCT group, respectively, compared to 20.2% in Control group. Both TNT approaches did not increase the incidence of surgical complications (6.0%, 8.1% and 10.9% in Control, CNCT and INCT, respectively), with anastomotic fistula and abdominal infection being of most concern. Conclusions: Both TNT approaches increased the probability of ≥ 3 acute toxicity grades and patients could tolerate 4 cycles of neoadjuvant chemotherapy. Both TNT approaches could achieve a higher proportion of downstage and CR rate. Clinical trial information: NCT04543695. Research Sponsor: None.

Consistency and heterogeneity of microsatellite instability (MSI) status in paired biopsy and surgical specimens of colorectal cancer: A necessity for MSI reassessment after treatment? First Author: Yuan Tang, Department of Pathology, West China Hospital, Sichuan University, Chengdu, China

Background: Microsatellite instability (MSI) plays a crucial role as a cancer immuno-molecular biomarker for decision making and tumor response assessment. However, currently, there is still a lack of available data on the impact of neoadjuvant therapy on MSI status, as well as validated data on standardized methods for MSI testing in small biopsy samples. The study aimed to investigate the concordance of MSI status between paired biopsy and surgical samples, as well as the impact of neoadjuvant therapy on MSI status using a novel MSI (MSI-NGS) panel. Methods: A total of 137 colorectal cancer (CRC) patients were enrolled for this study, of whom 116 with paired biopsy and surgical samples were analyzed. A custom MSI-NGS panel was employed and its performance was compared to MSI polymerase chain reaction (MSI-PCR), which served as the gold standard. Results: Out of the 116 cases, 112 patients showed consistent MSI status between biopsy and surgical samples, with an overall accuracy of 97% regardless of the detection method used. In the cases with MSI discrepancy (6 cases), 83% (5/6) of the patients showed a transition from MSS to MSI-H from biopsy to surgery. Interestingly, all eight patients who received neoadjuvant chemotherapy maintained an unchanged MSI status. However, in one patient who received adjuvant treatment and underwent a repeat biopsy after surgery, the MSI status exhibited alterations. Further analysis of clonal evolution revealed that this heterogeneity stemmed from the disappearance of the original clones and the emergence of new clones. Additionally, the NGS panel exhibited strong concordance with MSI-PCR and high accuracy, sensitivity and specificity with an AUC of 0.942 after rigorous validation. Conclusions: The study revealed a high concordance in MSI status between biopsy and surgical samples by employing a custom MSI-NGS panel for MSI status detection, providing reliable basis for further research in this field. Moreover, neoadjuvant chemotherapy seemed to have no impact on MSI status in our study, whereas postoperative adjuvant chemotherapy may influence changes in MSI status, highlighting the necessity of reevaluating MSI status after surgery. The findings also underscore the potential of NGS-based MSI detection as a valuable tool for clinical decision-making. Research Sponsor: None.

Enrichment of circulating helper-T (Th) and unswitched memory-B (NSwM-B) cell populations and responsiveness to immune checkpoint blockade (ICB) in microsatellite-stable (MSS)/mismatch repair-proficient (pMMR) colorectal cancer (CRC). First Author: Sebastian Meltzer, Akershus University Hospital, Norway

Background: The anti-tumor activity of ICB in MSS/pMMR-CRC is limited. However, recent studies have highlighted the possibility of inducing ICB responsiveness by oxaliplatin-based chemotherapy. The understanding of underlying mechanisms and identification of rational biomarkers are major focus areas in immuno-oncology. Methods: Patients with previously untreated colorectal metastatic cancers from four prospective clinical trials, anatomically assigned to the oxaliplatin-based standard Nordic FLOX regimen (control arm) or 2 FLOX cycles followed by 2 ICB (nivolumab) cycles in a repeat sequential schedule (experimental arm). Radiologic response assessment was done every 8 weeks, and the study arms received identical primary endpoint – median progression-free survival (PFS) 9.3 months. Experimental-arm patients at one study center had peripheral blood mononuclear cells (PBMC) prepared at study entry (V1), after the initial 2 FLOX cycles (V3), and after the succeeding 2 nivolumab cycles (V5). The PBMC were incubated with 19 cell-surface antibodies and analyzed by mass cytometry. Patients were categorized in PFS >9.3 months (improved, n = 7) or PFS <9.3 months (shortened, n = 6). Live cell clusters were identified by hierarchically applying automated 1D gates to the available lineage markers. After gating, all cells were assigned to soft clusters according to phenotypes. The cluster sizes were used to compute the differential abundance of immune-cell populations and a Peacock test was used to associate changes between the improved and shortened PFS groups. Results: Circulating CD4+ (Th) cells and CD27+IgD+ (NSwM-B) cells were concurrently enriched in the improved PFS group. After the initial 2 FLOX cycles (V3), median increase (from V1) was 2.89% (of lymphocyte count) for Th cells and 0.54% (of leukocyte count) for NSwM-B cells (p < 0.001). Continued responses occurred over the succeeding 2 nivolumab cycles (V5). At median increase was observed in the low-increase group compared to the high-increase group (log-rank p = 0.002). Conclusions: This unsupervised analysis of high-dimensional PBMC data from a limited case number revealed that circulating Th and NSwM-B cell populations may mediate ICB responsiveness invoked by short-course oxaliplatin-based chemotherapy in patients with adenomatous metastases from MSS/pMMR-CRC. Owing to weaknesses of such a post-hoc analysis, further studies are needed to confirm the generalizability of these findings. Clinical trial information: NCT03808353. Research Sponsor: Stand Up To Cancer.

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Genome-wide DNA methylation status to predict the efficacy of modified (m)-FOLFOXIRI plus cetuximab as initial treatment for RAS wild-type metastatic colorectal cancer: A biomarker study of the DEEPER trial (JACCRO CC-13AR). First Author: Kota Ouchi, Department of Medical Oncology, Tokushima University Hospital, Sendai, Japan

**Background:** Genome-wide DNA methylation status (GWMS) has been shown to be a predictor of therapeutic response to anti-EGFR antibody therapies. This study investigated the association between GWMS and clinical outcomes of first-line chemotherapy with anti-EGFR or anti-VEGF antibody agents for metastatic colorectal cancer (mCRC).

**Methods:** Tumor tissues of 621 patients enrolled in the JACCRO CC-13AR trial were embedded in paraffin and cut into 5-µm sections. DNA was extracted from formalin-fixed paraffin-embedded tissues and subjected to bisulfite conversion. Methylation-specific polymerase chain reaction (MSP-PCR) was performed to assess the methylation status of 274 high-risk CpG islands (CGIs) previously associated with poor clinical outcome in mCRC. Clinical data were obtained from the randomized phase II trial, DEEPER trial (JACCRO CC-13AR [NCT02515734]), in which patients were randomly assigned to m-FOLFOXIRI plus cetuximab (CET) arm and m-FOLFOXIRI plus bevacizumab (BEV) arm for treatment. Progression-free survival (PFS), overall survival (OS), depth of response (DR), and response rate (RR) were analyzed according to GWMS for each treatment arm.

**Results:** One hundred thirty-seven out of 227 patients enrolled in the JACCRO CC-13AR were analyzed. Of these, 122 (89.1%) and 15 (10.9%) were classified in the LMCC and HMCC, respectively. 66 were assigned to the CET arm including 7 HMCCs, and 54 were assigned to the BEV arm including 8 HMCCs. In the CET arm, PFS and OS of the LMCC were significantly longer than those of the HMCC (median PFS 14.3 vs. 4.0 months, HR 0.29, 95% CI: 0.16-0.52; median OS 42.1 vs. 13.6 months, HR 0.44, 95% CI: 0.23-0.83). There were no differences in DR and RR between the LMCC and HMCC (median DR 28.5% vs. 24.1%, P=0.45; median RR 75.0% vs. 73.0%, P=0.91). However, OS of the LMCC was significantly longer than that of the HMCC (median OS 72.1 vs. 24.6%, P=0.03). In contrast, in the BEV arm, there were no differences in PFS, DR, and RR between the two groups (median PFS 16.1 vs. 12.2 months, P=0.08; median DR 48.7% vs. 53.9%, P=0.39; RR 73.0% vs. 75.0%, P=0.91). However, OS of the LMCC was significantly longer than that of the HMCC (median OS 48.9 vs. 24.2 months, HR 0.39, 95% CI: 0.16-0.95, P=0.03).

**Conclusions:** This study showed that GWMS may be a prognostic marker for initial treatment in RAS wild-type mCRC. Also, GWMS correlates to the survival outcomes of m-FOLFOXIRI plus CET as initial treatment for RAS wild-type mCRC. Clinical trial information: 000018412. Research Sponsor: Japan Clinical Cancer Research Organization.

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Genomic alteration in sporadic adolescent and young adult-onset colorectal adenocarcinoma. First Author: Krittiya Korphaisarn, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

**Background:** Colorectal cancer (CRC) incidence is increasing in adults younger than 50 years. This study evaluated genomic alteration in adolescent and young adult (AYA) onsets of CRC patients who were aged between 18 and 39 years. The archived formalin-fixed, paraffin-embedded (FFPE) tissue samples that histologically confirmed adenocarcinoma with sufficient match repair tumors at Siriraj Hospital (Bangkok, Thailand) were extracted. Patients who clinically suspected familial adenomatous polyposis were excluded. Gene mutational analysis was performed by next-generation sequencing (NGS) using an Oncomine Comprehensive Assay Plus kit (Thermo Fisher Scientific, Inc., Waltham, MA, USA) and compared with previous reported molecular data in adult-onset CRC from our group. The top 5 mutations frequency observed were TP53, KRAS, FBXW7, PIK3CA, and SMAD4 mutations which were comparable to what reported in adult-onset CRC. However, FBXW7, PIK3CA, NOTCH1, FGFR3, ERBB2, and PTEN were reported more frequent in AYA group. No difference in number of KRAS, NRAS, and BRAF mutations among 2 groups. Table below shows key cancer genes mutation frequencies. **Conclusions:** This study is the comprehensive report hotspot mutations using NGS in sporadic AYA-onset sporadic CRC patients. The most commonly identified gene mutation frequencies among AYA-onset were similar to those reported in adult onset, except for FBXW7, PIK3CA, NOTCH1, FGFR3, ERBB2, and PTEN mutations that had a slightly higher frequency. Further studies on larger sample set for genetic and epigenetic landscape are required. Research Sponsor: None.

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Characterizing differential efficacy and phenotypic response to proteasome and survivin inhibitors in colorectal cancers using a high throughput organic tumor (BOT) screening. First Author: Dana Zuaiter, CerFlux, Inc., Birmingham, NY

**Background:** Conventional monolayer cell cultures and xenograft models, while useful and economical in early drug discovery, cannot predict clinical efficacy. Further, preclinical screening assays that rely on differential metabolic activity between separate control and treated wells are incapable of capturing phenotypic response and could overstate efficacy for cells with high rates of proliferation. Consequently, over 95% of anticancer agents that show efficacy in preclinical studies, fail in clinical trials. Recently, patient-derived organoid (PDO) models have been utilized in developing platforms to predict clinical efficacy of preclinical formulations. If successful, such predictive ex vivo technologies could revolutionize cancer treatment by reducing cost and time-to-market for new, more effective therapeutics. Objective: Characterize a novel bioprinted organoid tumor (BOT) high-throughput screening ex vivo platform for drug response prediction (DRP). Methods: Bioink for 3D printing BOTs was prepared with HT-29 cells, an established NCI-60 human colorectal adenocarcinoma cell line with known sensitivity to proteasome and survivin inhibitors. Bioink was deposited layer-by-layer on multiple substrates, in various geometrical configurations, and cured in stages to allow cells and matrix to self-assemble with limited degrees of freedom. BOTs were screened 24h and 48h after printing with proteasome inhibitor Bortezomib and survivin inhibitor YM-155. BOTs were evaluated 48h and 72h after treatment using immunofluorescence live/dead assay. Morphological phenotypic changes resulting from treatment were also recorded. Results: Proteasome and survivin inhibitors have been reported to inhibit proliferation and induce cell death in colorectal cancer cells. A dose dependent response was observed for both agents in our novel BOT HTS thereby validating the platform. In addition, characteristic self-assembly of HT-29 cells was observed to be disrupted at effective doses and at certain concentrations below the effective dose. Traditional ATP assays are incapable of recording such phenotypic modulation. Further, a higher proliferation profile was observed in untreated BOTs suggesting that use of independent control wells in traditional assays could overstate efficacy of treatment. **Conclusions:** Functional high-throughput ex vivo DRP technologies have the potential to transform cancer treatment – from bench to bedside – along the drug discovery to market roadmap for much needed novel anticancer agents. Research Sponsor: NSF.
Comprehensive genomic analysis of molecular residual disease based on circulating tumor DNA in patients with postoperative colorectal cancer. First Author: Qing-Hong Deng, Department of Gastrointestinal Oncology Surgery, The First Afiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, Fujian, China

Background: Despite receiving curative resection, a considerable percentage of colorectal cancer (CRC) patients still experience disease recurrence. The early detection of molecular residual disease (MRD) has the potential to improve risk assessment.

Methods: A total of 104 patients with stage I-IV CRC were enrolled, of which 259 serial plasma samples were collected. Multi-gene targeted sequencing was conducted on tumor and plasma samples to identify somatic variants. Results: Among the 104 patients, 14 cases had positive landmark MRD and 32 cases had positive longitudinal MRD. Patients with positive landmark MRD had significantly higher recurrence risk compared to those with negative landmark MRD (Hazard Ratio [HR]: 7.255; 95% CI: 2.877-18.647; P < 0.001). Similarly, positive longitudinal MRD was associated with increased recurrence risk (HR: 9.385; 95% CI: 3.085-28.556; P < 0.001), with a higher HR value. Positive MRD detection preceded CT confirmed recurrence in 85.7% of patients, with a median lead time of 198.5 days. In multivariate analysis, positive-MRD was the most significant prognostic factor for DFS. The combination of KRAS variant and MRD status improved the efficiency of prognostic prediction, the area under the curve value for the combination of MRD and KRAS was higher than MRD and KRAS. By analyzing the characteristic of ctDNA fragments, we found that mutation sites tended to be enriched in shorter cell free DNA (ctDNA) fragments. Conclusions: Our study demonstrated an excellent prognostic potential of circulating tumor DNA-based MRD detection among postoperative CRC patients, especially targeting the combination of KRAS variant and MRD improved the efficiency of risk stratification through MRD. This study may facilitate the incorporation of MRD and KRAS into prognostic prediction. Our study revealed that mutation sites tended to be enriched in shorter DNA fragments, providing valuable insights for future ctDNA detection method.

Research Sponsor: Natural Science Foundation of Fujian Province; National Science Foundation of Xiamen, China; Medical Innovation Project of Fujian Provincial Health Commission; Xiamen Natural Science Foundation General Project.

Clinical utility of serial circulating tumor DNA (ctDNA) to identify acquired resistance to anti-EGFR antibodies in metastatic colorectal cancer (mCRC). First Author: Jonathan M. Loree, BCDA, Vancouver Cancer Centre, Vancouver, BC, Canada

Background: Real-world evidence informing on the value of incorporating serial ctDNA into clinical practice is lacking. We aimed to explore the utility of serial ctDNA for identifying mechanisms of resistance and new targets for patients (pts) receiving anti-EGFR therapy for mCRC who had ≥1 alteration detected on a Guardant30 assay (Guardant Health) and subsequently had serial ctDNA assessments with known intervening therapies. We compared detection of new MAPK pathway alterations (RAS/ERBB2/RAF/VEGFR2/SW or indel, MET or ERBB2 amplification) among patients who initially lacked these alterations by whether patients received anti-EGFR antibody alone (panitumumab or cetuximab), in combination with chemotherapy, or if they had never received an anti-EGFR antibody between ctDNA assays. Patients with a subsequent ctDNA assay after therapy initiation were included for analysis of acquired alterations. Results: Of 2081 pts, 1308 (47%) harbored ≥1 MAPK alteration in their first ctDNA timepoint and were excluded from analysis. Of the remaining 1493 without a MAPK alteration prior to therapy, 588 (39.4%) had a MAPK alteration detected in a subsequent ctDNA timepoint. Among 447 of 1493 pts (31.8%) with subsequent exposure to anti-EGFR antibodies, acquisition of a MAPK alteration occurred in 229/447 (51.2%). This was more common (OR 2.01, 95% CI 1.61-2.51, P < 0.001) than in patients without exposure to anti-EGFR antibodies (359/1046 [34.3%]). Acquired MAPK alterations were more common among those receiving single agent antibodies (42/66, 63.6%) than anti-EGFR plus chemotherapy (187/381, 49.1%) (OR 1.82, 95% CI 1.05-3.08, P = 0.030). Patients with anti-EGFR antibody exposure were found to have higher blood TMB scores in the first assay after treatment compared to patients treated with chemotherapy alone (11.5 vs. 8.8 mut/MB, respectively; P < 0.001), with no significant blood TMB difference between those receiving single agent anti-EGFR versus anti-EGFR plus chemotherapy (median 12.4 vs. 11.5 mut/MB, P = 0.52). Patients who acquired MAPK alterations after anti-EGFR therapy had higher blood TMB scores compared to those who did not acquire MAPK (5.5 vs. 4.2 mut/MB, respectively; P < 0.001). Conclusions: In this large cohort of pts with mCRC and treatment information, we demonstrate serial ctDNA identified a large proportion of patients acquiring resistance alterations that may impact response to future therapies. These results suggest serial ctDNA analysis may provide additional molecular insights for patients receiving anti-EGFR therapy and inform future anti-EGFR rechallenge strategies.

Research Sponsor: Guardant Health.

Clinical utility of upfront circulating tumor DNA (ctDNA) genotyping to guide first-line therapy in patients (pts) with metastatic colorectal cancer (mCRC). First Author: Yu Aoki, Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: The clinical utility of upfront ctDNA genotyping is not established in treatment (tx)-naive pts with mCRC. Methods: GOZILA is a nationwide plasma genomic profiling study using Guardant360 CDx for advanced solid tumors. We assessed ctDNA molecular profile and its association with treatment efficacy in pts with mCRC who were enrolled in GOZILA from January 2018 to July 2022 and underwent ctDNA genotyping before initiation of first-line systemic tx. ctDNA fraction was defined as the maximum variant allele frequency of somatic alteration and pts were classified into three groups based on ctDNA fraction: low (<1%), middle (1% and <10%) and high (≥10%) ctDNA fraction groups. Results: This study included 418 pts with mCRC receiving upfront ctDNA genotyping. Median turnaround time of ctDNA test was 7 days, comparable to standard-of-care (SOC) tissue RAS/BRAF testing (7 days) and microsatellite instability (MSI) testing (8 days). Pathogenic alterations were detected in 384 pts (92%), and concordance rates for RAS and BRAF mutation (mut) compared to SOC tissue-based testing were 91% and 97%, respectively.

Based on biomarkers identified by ctDNA genotyping, 142 (40%) pts were treated with matched targeted tx: anti-EGFR antibody for RAS/RAF wild-type (n=137), BRAF inhibitor for BRAF V600E mutation (n=4), and anti-PD-1 antibody for MSI high (n=1). Low, middle, and high ctDNA fraction groups included 87, 97 and 234 pts, respectively, and had significantly different median progression-free survival (PFS) (P = 0.01, table) and overall survival (OS) (P = 0.01, table). In 13 pts who repeated ctDNA test before second-line tx, those with elevated ctDNA fraction compared to upfront ctDNA had significantly shorter PFS (median, 3.8 vs. 8.1 months; HR, 5.7; 95% CI, 0.9 to 35.1) and OS (median, 8.2 vs. 17.4 months; HR, 11.3, 95% CI, 1.2 to 105.9) of second-line tx that those who did not acquire MAPK alterations. Conclusions: Our study revealed that acquired actionable genetic alterations in pts with mCRC. ctDNA fraction in upfront ctDNA was significantly associated with efficacy of first-line tx and ctDNA fraction monitoring may be useful in determination of subsequent tx.

Research Sponsor: SCRUM-Japan Foundation.
Tumoral microbial and pathway alterations associated with young-onset rectal cancer and its response to therapy.

**Methods:** We acquired tumor DNA and RNA from patients with young-onset rectal cancer (YORC) and performed whole transcriptomic and whole genome sequencing for 53 patients with YORC. The patients were grouped into two categories, with young-onset rectal cancer (YORC) (age <50 years) and older-onset rectal cancer (LORC) (age ≥50 years). We investigated the association of microbial and immune markers with response to therapy, as well as the impact of these factors on survival outcomes.

**Results:** We observed several unique bacterial associations with response to therapy, including an association with the bacterial marker of response to neoadjuvant therapy in LORC. Additionally, several unique bacterial markers were identified in LORC tumors compared to TAN tissue. We also noted distinct microbial associations related to response to therapy in YORC, including the unique function of bacterial pathways in these tumors.

**Conclusions:** Our findings suggest that the integration of microbial and immune markers into risk stratification schemes for colorectal cancer could improve treatment outcomes for patients with YORC.

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**Background:**

There is a need to improve current risk stratification of stage II and III colorectal cancers through incorporation of the digital pathology biomarker QuantCRC. The purpose of this study is to examine whether integration of QuantCRC, an AI-based digital pathology biomarker utilizing hematoxylin and eosin-stained slides, provides improved risk stratification over current American Society of Clinical Oncology (ASCO) guidelines.

**Methods:**

ASC0 and QuantCRC-integrated risk schemes were applied to an observational cohort of 1,068 stage II and III CRCs. The QuantCRC-integrated scheme utilizes pT3 vs. pT4 and QuantCRC-derived risk groups. The stage III integrated scheme utilizes pT1-3 vs. pT4, pN1 vs. pN2, and QuantCRC-derived risk groups. Performance metrics included log-rank test, hazard ratios, and Somers’ rank correlation.

**Results:** Integration of QuantCRC provides improved risk stratification compared to the ASC0 scheme for stage II and III CRC. The QuantCRC-integrated scheme placed more stage II tumors in the low-risk group compared to the ASC0 scheme (69.3% vs. 60.4%) without decreasing 3-year RFS. The QuantCRC-integrated scheme provided larger hazard ratios for both intermediate-risk (3.04, 95% CI 0.81-5.10 vs. p=0.001) and high-risk (4.62, 95% CI 2.02-10.61, p=0.0003) groups compared to ASC0 intermediate-risk (2.09, 95% CI 1.21-3.63, p=0.006) and high-risk (3.08, 95% CI 1.57-6.01, p=0.001) groups. The QuantCRC-integrated stage III CRCs identified a small group of 80/581 (15.4%) CRCs at high risk of recurrence with HR of 4.08 (95% CI 2.68-6.23) compared to 6.5x10^-1 (1) compared to a HR of 2.94 (95% CI 1.72-3.83, p=3x10^-11) for 228/518 (44.0%) high-risk CRCs in the ASC0 scheme. QuantCRC-integrated risk groups remained prognostic in stage III CRCs when stratified by presence or absence of any adjuvant chemotherapy. No difference in RFS were seen in QuantCRC-integrated low-risk and intermediate-risk stage III CRCs stratified by 3 months of oxaliplatin-based adjuvant chemotherapy suggesting that these two groups can be treated with 3-months of adjuvant therapy.

**Conclusions:** Integration of QuantCRC into risk stratification provides a powerful predictor of RFS that has potential to guide subsequent treatment and surveillance.

**Research Sponsor:** None.

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**Conclusions:** Integration of QuantCRC into risk stratification provides a powerful predictor of RFS that has potential to guide subsequent treatment and surveillance.

**Research Sponsor:** None.
Comparison of colorectal cancer (CRC) characteristics across genetic ancestries: Implications for early cancer detection (ECD). First Author: Parvathi Gupta, Albert Einstein Cancer Center, New York, NY

Background: Blood-based ECD has the potential to reduce mortality rates by improving strategies for, adoption of, and adherence to screening. A deeper understanding of the cancer genomic landscape across genetic ancestries will aid comparable detection performance across a broad population. We evaluated the mutational landscape in patients with CRC across genetic ancestries. Methods: 16,080 de-identified patients with stage I-IV CRC who had personalized, tumor-informed commercial cDNA testing (Signatera) based on whole exome sequencing (WES) were included. Genetic ancestry determined via supervised local ancestry inference (pmd36042291) included African (AFR), East Asian (EAS), European (EUR), Latino (LAT), and South Asian (SAS). Patients assigned to a single ancestry were included (except SAS due to small cohort size). Some singlenucleotide variations (SNVs) from WES were used for mutational signature inference. EUR was the reference group for standard statistical tests with corrections for multiple hypothesis testing. Results: A single genomic ancestry was assigned for 16,257 (99.2%) patients (AFR n=1679, 10%, EUR n=10526, 64%; LAT n=1291, 1%; SAS n=184, 1%). Across AFR, EUR, EAS, and LAT, approximately half of patients were male (range, 47-54%) and most were aged >50 years. Microsatellite instability (MSI) rates were significantly higher in EUR (14.5%) vs AFR (11%, p < 0.001), EAS (6%, p < 0.001), and LAT (11%, p = 0.002). Compared to EUR (range 0.073-2.75 mutations/MB, p < 0.001), and lower in LAT (0.053-4.76 mutations/MB, p < 0.001). The POL2 hyper-mutator signature was seen in 1.2% of all patients and in 7.6% of all hyper-mutated cases. Patients with the POL2 signature were less common in EUR (1.1%) vs AFR (2%, p < 0.001). There were significant differences in the frequency of driver mutations in AFR, EUR, KAS, TPS3, and PAK1/CA between EUR and the other ancestry groups in both MSI and MssS tumors (Table). Median exposure levels to alkylation were higher in EAS vs EUR.

Conclusions: These data confirm previous AFR results in AFR populations, and reveal novel differences in the EAS and LAT populations. Findings from this study may provide information for developing risk stratification tools, screening strategies for the early detection of CRC, and provide rationale for precision treatment based on ancestry. Research Sponsor: None.

Liver steatosis and fibrosis as independent prognostic factors affecting survival in colorectal cancer with liver metastases. First Author: Nikhil Gupta, Case Western Reserve University, Cleveland, OH

Background: Colorectal cancer is one of the leading causes of cancer-related death, and the liver represents the most common site of metastases. Greater depth of tissue invasion and lymph node metastases (more advanced T and N stage) are associated with increased risk of liver metastases, but how co-pathologies of the liver associate with disease progression and survival are not known. Further, prognostic factors associated with overall survival in patients with colorectal liver metastases (CRLM) remain poorly understood. Clinical factors affecting colorectal cancer survival are often complicated by pre-existing liver comorbidities, such as pre-existing fibrosis or steatosis, may impact the pathogenesis of CRLM and thus the clinical prognosis. Current literature is mixed about whether prior steatosis and fibrosis contribute significantly to CRLM pathogenesis and prognosis. The purpose of this study is to evaluate whether liver steatosis and fibrosis impact outcomes in patients with CRLM. Methods: All CRLM cases (n = 197) that underwent surgery between 2003 and 2007 from The Cancer Imaging Archive were included in our study cohort. For each clinical covariate, we generated a univariate model for overall survival and those meeting a modest predictive threshold (p < 0.15) were included in a multivariable model. These included: presence of major comorbidity, chemotherapy preceding resection of liver metastases, clinical risk score, presence of extracranial disease at time of diagnosis, presence of steatosis on CT imaging, percentage of residual tumor after treatment, and presence of fibrosis on CT. All statistics were performed in R (v.2022.12.0). Results: A multivariable Cox proportional hazards model identified four statistically significant clinical factors predictive of overall survival: clinical risk score (HR = 1.60, p = 0.002), presence of extracranial disease (HR = 2.33, p = 0.027), presence of steatosis (HR = 0.51, p = 0.005), and fibrotic proportion of liver tissue less than 40% (HR = 2.63, p = 0.033). There were also four statistically significant clinical factors predictive of disease-free survival in the liver: chemotherapy preceding resection of liver metastases (HR = 2.26, p = 0.002), presence of extracranial disease (HR = 2.18, p = 0.024), presence of steatosis (HR = 0.49, p = 0.003), and fibrotic proportion of liver tissue less than 40% (HR = 2.74, p = 0.016). Conclusions: Our findings suggest that increased steatosis and fibrosis, as assessed by CT scans, are paradoxically protective in CRLM, showing longer disease-free survival and overall survival rates. We hypothesize that liver steatosis and steato-fibrosis may be part of the control mechanisms in the liver, impairing tumor progression in this milieu. Further research is needed to assess how non-neoplastic co-pathologies resulting in biophysical changes affect tumor growth and overall survival. Research Sponsor: None.
Association of class II and III BRAF mutations with EGFR blockade therapy response and representation of molecularly distinct subgroups of BRAF mutations in MMPI proficient CRC. First Author: Ibrahim Haili Sahin, University of Pittsburgh Medical Center, Pittsburgh, PA

**Background:** BRAF mutations (mts) represent a highly heterogeneous group of molecular alterations seen in colorectal cancer (CRC). Class I BRAF mts (V600) render aggressive biological activity to CRC and poor response to anti-EGFR inhibitors. Currently there are limited data on clinical and molecular features of class II and III BRAF mts. In this study, we investigated the clinical and molecular characteristics of BRAF mts in these classes and their impact on survival outcomes in a large cohort of patients (pts) with mismatch proficient (pMMPI) CRC. 

**Methods:** A total of 1857 PMMRCRC CRC specimens were profiled by next-generation sequencing (592-gene, NextSeq; WES, WTS NovaSeq) (Carns Life Sciences, Phoenix, AZ). BRAF mts were detected by NGS and classified using published literature (Sahin et al, 2021). Interferon gamma signature and MAPK pathway activity score (MAPS) were calculated using RNA expression data (TPM). Real-world overall survival information was obtained from insurance claims and calculated from tissue collection to last contact, while post-treatment survival from first of treatment to last contact. KM estimates were calculated for molecularly defined cohorts. Significance was determined as p values of <0.05. Results: A total of 930,105, and 262 pts with class I, II, and III BRAF mts were identified. Pts with class III BRAF mts were significantly more common among younger pts (age ≥45) compared to class I and II (8.8% vs. 4.8%, 1.0 % respectively; P<0.05). Class I BRAF mts were significantly enriched with consensus molecular subtype 1 (CMS1) (Class I, II and III: 44% vs. 17% vs. 18%) while class I and III BRAF mts were more often CMS2 subtype (canonical) compared to class I (2%, 30% and 3%, p<0.05). Class I BRAF and KRAS/RAF mts were mutually exclusive, while KRAS mts incidences were 15% and 22% for class II and class III, respectively. NMAS mts prevalence were 8% and 12%, respectively. MAPS score significantly lower for class I (0.32, arbitrary unit) compared to class I (p<0.05), but similar MAPS scores were seen in class I and II (1.3 versus 1.8). No difference in interferon gamma signature was noted between classes. Pts with class II and III mts had significantly better overall survival compared to patients with class I mts (HR:0.69, 95%CI:0.597-0.804, p<0.0001) and slightly worse overall survival compared to wild-type BRAF pts. (HR: 0.85, 0.75: 0.96-0.01 0.32). Among pts treated with anti-EGFR, pts with class II and III BRAF mts had significantly better post-anti-EGFR survival compared to class I BRAF mts (HR 0.49 C 0.32-0.76 p<0.001) and similar survival compared to those with wild-type (p=0.1). Class I and III BRAF mts are associated with improved outcomes with EGFR blockade and represent a distinct biological subgroup of pMMPI CRC. Class III BRAF mts have lower MAPK activation, consistent with the pattern of kinase-dead mutations. Research Sponsor: None.

**Conclusions:** BRAF mts are associated with improved outcomes with EGFR blockade and represent a distinct biological subgroup of pMMPI CRC. Class III BRAF mts have lower MAPK activation, consistent with the pattern of kinase-dead mutations. Research Sponsor: None.

Clonal hematopoiesis of indeterminate potential (CHIP), treatment outcomes and adverse events in gastrointestinal cancers: A pooled analysis of clinical trial and real-world data. First Author: Tharani Krishnan, BC Cancer - Vancouver, Vancouver, BC, Canada

**Background:** Clonal hematopoiesis of indeterminate potential (CHIP) is the acquisition of somatic mutations leading to clonal expansion of hematopoetic stem cells and is a common incidental finding in circulating tumor DNA (ctDNA). Infection from these cells or a reduced marrow reserve may impact treatment outcomes or adverse events. We investigated the incidence of CHIP in ctDNA from patients with gastrointestinal (GI) cancers and explored its association with outcomes and adverse events (AEs). 

**Methods:** We collected ctDNA results from a local prospective metastatic colorectal cancer (mCRC) cohort (PREDICT-C) and ctDNA data from two randomized trials: CCTG CO.26 (dualavumab + tremelimumab [D+T] or best supportive care [BSC] in mCRC) and CCTG PA.7 (PAMjcbine citable: [B] vs [T] or atezolizumab + bevacizumab [A+T] or single agent [S] in mCRC). CHIP+ was defined as the presence of a variant of ≥2% variant allele frequency annotated in the ctDNA report in any of the genes DNMT3A, TET2, ASXL, and ATM, and not annotated as germine by respective sequencing platforms. The first line of treatment after ctDNA was reviewed, and grade ≥3 or dose-limiting adverse events were documented. Results: The prevalence of CHIP varied from 10% to 18% (see table). CHIP+ patients were older than CHIP- in the CO.26 cohort (p<0.001), and ECOG was higher in CHIP+ patients in the PREDICT-L cohort. There was no difference between CHIP+/ patients with regards to sex. DNMT3A was the gene most frequently mutated in all three cohorts. There was no significant difference in PFS or OS between the CHIP+/- groups, both in those treated with chemotherapy (Chemother) or immunotherapy (IM). The most common AEs were rash, GI toxicities and bleeding/clotting abnormalities. There was no significant difference in the rates of AEs between the CHIP+/- groups for those treated with Chemother or IM. Conclusions: CHIP is a common alteration in ctDNA but did not impact PFS or OS, or the chance of developing an AE. Research Sponsor: AstraZeneca (sponsored the CO.26 and PA.7 clinical trials).

**Poster Session**

**Preclinical analysis and clinical validation to identify biomarkers of regorafenib efficacy in patients with metastatic colorectal cancer. First Author: Mitsuksuki Suenaga, Clinical Oncology, Tokyo Medical and Dental University, Tokyo, Japan**

**Background:** In the identification of biomarkers for anticancer drugs, the lack of objectivity in the selection of candidate factors makes it difficult to interpret the mechanism. We performed preclinical analysis and translational validation study to identify the candidate cytokides for regorafenib efficacy in metastatic colorectal cancer (mCRC) patients. Methods: As a first preclinical process, we selected candidate cytokines according to our gene chip analysis using a panel of human cancer cell lines (JFCR39). We then validated predictive value of the cytokines in mCRC patients re- ceiving regorafenib (discovery, N=54) and FTD/TPI (control, N=16). Blood samples were obtained at baseline (BL), before second cycle (2nd) and progressive disease (PD), and cytokine levels were measured using ELISA. Finally, we measured changes in cytokine levels and cell number in colorectal cancer cell lines treated with regorafenib. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier curves. Results: Our gene chip analysis showed association between high matrix metalloproteinase (MMP)-14 expression and high sensitivity to regorafenib, and the MMPs pathway was examined in blood samples. In the discovery cohort, high MHP14 levels at BL (mean 2.66 ± 1.91 ng/mL, P=0.006) and PD (mean 2.34 vs. 1.71 ng/mL, P=0.02) were associated with tumor shrinkage, and high MHP14 levels at PD were associated with lower changes. These findings were not observed in the control cohort, but MMP9 levels decreased at 2nd in 94% of patients. In a regorafenib-sensitive cell line, HT29, MHP14 levels were increased whereas there was no change in regorafenib-resistant HCT15 cells. Conclusions: Our preclinical data-based translational validation study suggests that MHP14 and MHP9 may serve as a prognostic marker of regorafenib, and the results also provide insight for novel combination therapy with anti-MMP9 agent or FTD/TPI. Research Sponsor: JSPS KAKENHI.
**LMTK3 gene expression and the molecular landscape of colorectal cancer (CRC).**

First Author: Leyes Torres-Gonzalez, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

**Background:** Lm Not1 kinase 3 (LMTK3) plays a critical role in multiple cellular pathways such as Wnt signaling, KIT modulation, and the estrogen receptor pathway. We previously reported that LMTK3 gene polymorphisms are associated with clinical outcome in patients with CRC, and that LMTK3 and estrogen-mediated signaling play a crucial role in CRC tumorigenesis in vitro. Here, we aimed to characterize the molecular features associated with LMTK3 gene expression in CRC.

**Methods:** 20:219 CRC were tested at Garis Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS). Top quartile transcripts per million (TPM) for LMTK3 expression (Q4) were considered high while bottom quartile (Q1) genes were considered low. LMTK3 expression was assessed using the Firehose (https://firehose.alliancefound.org) digital gene expression tool. T-cell infiltrated (integrated firehose [IFH] score) gene expression was highest in left-sided (0.98 median TPM) followed by right-sided (0.96) and lowest in rectal tumors (0.92). No difference in patient sex distribution was observed between Q1 and Q4 cohorts. Overall, LMTK3 Q1 was associated with TMB-high (± 10 Mut/Mb, 11.4 vs 8.7%) and dMMR/MSI-H (8.1 vs 4.6%) (p < 0.0001); however, these associations were no longer significant in pMMR/MSI tumors. In the pMMR/MS cohort, LMTK3 expression was highest in CSM4 (1.9 median TPM) followed by CSM2 (0.98), CSM1 (0.88), and lowest in CSM3 (0.70, all intergroup p < 0.05). LMTK3 high showed differences in rates of mutations and copy number alterations (CNA) in several genes, including higher mutation rates of APC, TP53, and CDX2 DNA, while lower mutation rates of KMT2A/DAX1, ATM, SMAD4, RNF43 and AMER1 in the overall cohort (p < 0.05). In the pMMR/MS cohort, the associations with APC, TP53, SMAD4 and ATM mutations and CDX2 DNA still held true (p < 0.05). High LMTK3 was associated with higher immune CI in the TME, including B cells, CD4+ T cells, CD8+ T cells, monocytes, DCs, natural killer cells, while D16 and Tregs were lower regardless of tumor MSI status (fold change: 0.83-2.4, all p < 0.001). The IFH score was significantly lower in LMTK3 Q4 while the TIS score was significantly higher in LMTK3 Q4 (p < 0.001).

**Conclusions:** Our data show a strong association between LMTK3 gene expression and different molecular features detected in the TME immune cells within colorectal tissues. These findings suggest that LMTK3 may be an important molecular factor that plays a role in determining the composition of the TME; thus targeting LMTK3 could represent a novel strategy in selected CRC subgroups.

Research Sponsor: National Cancer Institute; Gloria Wunderl Foundation; Donn Family Foundation; Gengo Gregence Pancreas Research Fund; San Pedro Peninsula Cancer Council; Daniel Butler Research Fund; V foundation for cancer research; Victoria and Philip Wilson Research Foundation; Fong research project; Ming Hsieh research fund.

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**Outcomes with immunotherapy between Lynch syndrome vs non-Lynch syndrome microsatellite instability-high colorectal cancer.**

First Author: Cody Eislinger, Department of Internal Medicine, Mayo Clinic Arizona, Phoenix, AZ

**Background:** Alterations to mismatch repair (MMR) genes such as MLH1, MSH2, MSH6, and PMS2, can lead to microsatellite instability-high (MSI-H) tumors. MMR mutations in Lynch Syndrome can also be a result of somatic mutations occurring within MSI-H CRC. Here, we aimed to characterize the molecular features associated with outcomes resulting in MSI-H malignancies. Treatment with immune checkpoint inhibitors (ICIs) have been shown to improve survival in such patients (pts) compared to systemic chemotherapy. However, there is a paucity of information in the literature with respect to outcomes of pts with germline vs somatic MMR mutations in MSI-H colorectal cancer. The presence of an associated BMN mutation confers resistance to chemotherapy in pts with CRC, however data regarding outcomes with immunotherapy in such pts with MSI-H CRC is lacking.

**Methods:** Pts records from the Mayo Clinic (AZ, MN, FL) between 2008-2023 denoted as MSI-H CRC, were included for retrospective review. Pt demographics, treatment courses, and genomic profiles were collected. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method. Outcome differences between sub-groups were accessed with the log rank test and univariate analyses were assessed with Cox-regression.

**Results:** A total of 81 pt records were identified (n = 18 LS, n = 63 non-LS). Stage IV disease was found in 28% of LS pts vs 59% of non-LS pts at diagnosis. Pemolizumab was the most common ICI selected for metastatic CRC pts for both LS and non-LS pts (65% vs 94%) with median treatment duration for each group 11.7 vs 8.8 months. There were no differences in OS or PFS for any stage between LS vs non-LS. Median OS for all patients was 82 months. For all stage IV patients, median OS was 44 months, and median PFS was 19 months. Interestingly, for stage IV pts treated with immunotherapy, tumors that harbored a BRAF V600E mutation (n = 21) vs BRAF wild type (n = 20) had a significantly lower median OS 19 vs 113 months (HR = 2.69, p = 0.043) as well as median PFS 12 vs 95 months (HR = 2.48, p = 0.041).

**Conclusions:** In this study, we found that patient treated with ICIs have similar outcomes in the presence of germline vs somatic MMR mutations in MSI-H CRC. The presence of an associated BRAF V600E mutation, which occurs in non-LS MSI-H CRC conferred worse outcomes. Research Sponsor: None.
Results: ctDNA testing was successful in 222/228 pts (table). The median follow-up was 15 months (range 3-37). Of 156 pts (68.6%) with a clear ctDNA+ test of 1 ctDNA+ test of 1 test, 49.2% (29/59) cleared ctDNA with 79.3% of clearances on or after therapy. Between ctDNA clearers and non-clearers, RR were 72.4% vs. 93.3%, mRFS 7.6 mo (HR 0.3, p=0.001) and mOS NR vs. 48.4 mo (HR 0.6, p=0.001). No significant associations existed between initial MTM/mL and tumor types (p=0.6), relapse status (p=0.2), or number of relapse sites (p=0.4). Conclusions: ctDNA is a prognostic tool able to detect early relapse with high accuracy in GI cancers. The initial MTM/mL, in ctDNA+ pts did not correlate with tumor histology or relapse patterns. Pts clearing ctDNA tended to have improved outcomes; however, RRs were higher than anticipated. More pts and longer follow up will help characterize the performance of ctDNA across rarer GI subtypes.

Research Sponsor: None.

The mechanisms of cancer-associated adipocytosis promoting colorectal cancer peritoneal metastasis via FBKP5/UCP1-mediated lipid metabolism reprogramming. First Author: Yue Zhang, Department of Gastroenterology, Guangdong Provincial People’s Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong Province, China; the Science and Technology Planning Project of Ganzhou, National Key Clinical Specialty Construction Project; Science and Technology Planning Project of Guangdong Province, China; the Science and Technology Planning Project of Guangdong Provincial People’s Hospital; CSOC-Roche Cancer Research Foundation; CSOC-Haosen Research Foundation.

Background: Colorectal cancer (CRC) is a prevalent malignant tumor globally, with peritoneal metastasis as a significant late-stage dissemination pathway, severely impacting patient prognosis. Recent research increasingly suggests the critical role of lipid metabolism within the tumor microenvironment in tumor progression. Cancer-associated adipocytosis (CAAs), a vital component, contribute to tumor progression, yet the exact metabolic mechanism remains unclear. We aim to explore the role of CAAs in CRC peritoneal metastasis and their specific regulatory mechanisms. Methods: In this study, we analyzed clinical samples from 312 CRC patients to assess the expression levels of FBKP5 and UCP1 proteins in tumor-adjacent tissues. Purified exosomes from co-cultured adipocytes and tumor cells, along with exosomes from normal tumor cells, underwent miRNA profiling via sequencing to evaluate exosomal miR-200-3p expression. We established FBKP5 stable knockdown (FBKP5-KD) transgenic mice models, organotypic co-culture models, and patient-derived xenograft (PDX) models. Through experiments involving metabolomics, mass spectrometry, immunoprecipitation, western blotting, and qPCR, we investigated the role of the miR-200-3p/FBKP5/PARP1/UCP1 signaling pathway in CAAs in CRC peritoneal metastasis.

Results: After co-culturing adipocytes and tumor cells, we observed brown adipocyte differentiation, resulting in significant downregulation of FBKP5 protein expression. FBKP5 KD showed a significant increase in UCP1 expression. Tumor cells highly expressed miR-200a-3p, released via exosomes into the tumor microenvironment and internalized by adipocytes. Within adipocytes, miR-200a-3p orchestrated metabolic reprogramming, with 79.3% of clearances on or after therapy. Between ctDNA clearers and non-clearers, RR were 72.4% vs. 93.3%, mRFS 7.6 mo (HR 0.3, p=0.001) and mOS NR vs. 48.4 mo (HR 0.6, p=0.001). No significant associations existed between initial MTM/mL and tumor types (p=0.6), relapse status (p=0.2), or number of relapse sites (p=0.4). Conclusions: ctDNA is a prognostic tool able to detect early relapse with high accuracy in GI cancers. The initial MTM/mL, in ctDNA+ pts did not correlate with tumor histology or relapse patterns. Pts clearing ctDNA tended to have improved outcomes; however, RRs were higher than anticipated. More pts and longer follow up will help characterize the performance of ctDNA across rarer GI subtypes.

Research Sponsor: None.

Identification of dMMR in metastatic colorectal and non-colorectal cancers in a private Mexican institution. First Author: Geovanna Filió, Merck, Mexico City, Mexico; the Science and Technology Planning Project of a private Mexican institution.

Background: DNA mismatch repair (dMMR) repair is a process in which normal cells maintain their original genomic information avoiding errors in mismatched nucleotides or base modifications from recombination processes. The failure of this process could drive carcinogenesis due to increased mutation rate as well as high microsatellite instability. It is estimated that the global average prevalence of dMMR/MSI-H across tumor types and stages is approximately 16%, with higher rates reported for early stages. However, the prevalence for colorectal (CRC) and non-colorectal cancers in this biomarker in Mexico has not been reported. Objective: To explore the prevalence of dMMR in metastatic CRC (mCRC) and non-CRC (gastric, esophageal, and endometrial cancer) from a private Mexican institution. Methods: In this retrospective study, the dMMR status of 215 samples was analyzed from a primary database of stored biopsies from patients diagnosed with metastatic CRC, endometrial cancer, and non-CRC between January 2017 and December 2020. 65 records had information about MMR status.

Results: The prevalence of dMMR was stratified by age and gender and expressed as frequencies. Statistical analysis was conducted in SPSS. Results: dMMR was found in 18.5% (N=27) endometrial cancer cases, 12.7% (N=150) of CRC cases, and 8.3% (N=24) of gastric cancer cases. However, it was not detected in any cases of esophageal cancer (N=14) in CRC, we found a higher percentage of incidence in men than in women, 15.6% (n=14/90) vs. 8.3% (n=5/60) respectively. By age groups, the highest total percentage (20%) was observed among those 41-50 years old. The age group with the lowest dMMR was 21-40 yo, with 7.7% of CRC patients over 91 yo (n=3), were dMMR.

Conclusions: Even though this data is not representative for the entire Mexican population, it provides preliminary prevalence dMMR estimates for some key cancers. Additional research is needed to give the limited sample sizes available for non-CRC. Research Sponsor: MSD; Mexico.

Benchmarking mismatch repair testing for patients with cancer receiving immunotherapy. First Author: Elias Bou Farhat, Brigham and Women’s Hospital, Boston, MA.

Background: Mismatch repair deficiency (dMMR) serves as a theranostic marker for directing immune checkpoint inhibitor (ICI) treatment across various cancer stages and lines of ICI treatment. The College of American Pathologists recommends that the (mCRC) as the primary approach for assessing mismatch repair (mMR) testing in colorectal (CRC) and endometrial cancer (EC) patients. An alternative method involves genetic evaluation of microsatellite instability (MSI). Previous studies have shown that resistance to immune checkpoint inhibitors (ICIs) may occur due to inaccurate MSI or MMR IHC status determination. Accurate assessment of MMR status is critical for treatment decision-making. Methods: We hypothesized that tumor-only next generation sequencing (NGS) for MMR mutation signature assessment for identification of MMR-D tumors is more sensitive than MMR IHC testing. Using a standardized, clinically validated, validated, NGS mutation signature, we line-of-the-oncopanel assay at DFCI/BWH, we compared the concordance in MMR determination between NGS and IHC. We then evaluated a subset of ICI-treated patients to assess the clinical implications of these findings. Results: 1655 colorectal cancer (CRC) and endometrial carcinoma (EC) patients who had both NGS MSI (NGS-D = deficient or NGS-P = proficient) and MMR IHC (IHC- = absent or IHC+ = intact) assays performed were assessed. Discordant NGS/IHC results were identified in 1% of CRC and 5% of EC cases that were IHC+. Importantly, patients with discordant NGS-D/IHC+ (median OS: not reached [NR], 95% CI, 9.9 months-NR; median TTF: 44.4 months, 95% CI, 4.1-NR) and concordant NGS-D/IHC+ results, showed a similar overall survival and time to treatment failure with ICI treatment (p=non-significant) which contrasted with results for patients with discordant NGS-D/IHC- results (median OS: 14.9 months, 95% CI, 7.3-24.6; p-value 0.0025 and < 0.0001; median TTF: 5.0 months, 95% CI, 3.2-7.3; p-value 0.0014 and < 0.0001). Patients with EC or CRC and discordant NGS-D/IHC+ results had better survival when treated with ICI-based regimens, compared to those who received non-ICI treatments (p=0.54 and 0.037). Conclusions: In 2022, 178 poster session. With 65,955 CRC cases were diagnosed in the USA. Evaluating our findings to this larger population, use of NGS mutational signature analysis instead of IHC would amount to about 1510 additional MMR-D CRC cases and 3297 additional MMR-D endometrial cancers identified each year for whom first-line ICI therapy is preferred. Our findings support reporting of testing guidelines and recommendions for diagnostic testing of MMR to incorporate both IHC and targeted NGS tumor panel testing using sensitive and specific mutation signature calling algorithms. Larger prospective studies are warranted to confirm these findings in patients with mCRC and mEC treated with ICIs. Evaluation of this approach in other cancer types is also warranted. Research Sponsor: None.
Multiomic analysis for minimal residual disease detection: Addressing challenges in stage II-III colon cancer from COSMOS-CRC-01. First Author: Yoshikaz Nakamura, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan.

Background: A considerable number of patients with stage II-III colon cancer experience disease recurrence following definitive treatment while others may receive unnecessary toxicity from adjuvant chemotherapy. Minimal residual disease (MRD) detection through ctDNA analysis has been evaluated without reliance on tissue which can be time-consuming and logistically challenging. Methods: COSMOS-CRC-01 is an ongoing biomarker study that enrolled patients with resectable stage II-III colorectal cancer between January 2020 and April 2021. Plasma samples and clinical data were collected 28 days post-surgery and every 3 months for up to 2 years alongside radiographic imaging. Samples were tested on the Guardant Reveal Infinity Oncology Platform for MRD detection. This analytically validated multiomic NGS assay interrogates >700 genes and ~15Mb of methylated regions. A bioinformatics algorithm trained for CRC detection classifies each sample as ctDNA detectable or undetectable based on a predefined statistical likelihood threshold and returns quantitative tumor fraction. The primary endpoint was time to recurrence (TTR) based on ctDNA detection status.

Results: This subgroup analysis evaluated 801 post-surgical plasma samples (464 each, mean initial 1mg, 96% passed QC) from 136 patients with R0 resected stage II-III colon cancer with a median follow-up of 28 months. ctDNA detection at Day 28 post-surgery and following adjuvant chemotherapy were both associated with significantly shorter TTR (p = 0.001; Table). Sensitivity with serial monitoring was 80% (95% CI, 56.3-94.3%), with a median lead time of 5.3 months. Sensitivity was highest for detection of locoregional (2/2), brain (1/11), liver (7/7), or multiple (3/3) metastasis compared to isolated lung (2/2) or peritoneal (1/3) metastasis. Tumor fraction increased as expected in samples collected closer to the time of radiographic detection. Three resected patients had KRAS G12V variants detected in ctDNA prior to recurrence, suggesting the potential of early intervention with targeted agents. Among 553 post-recurrence samples, sample specificity was 97.3% (95% CI 95.6-98.9%). Conclusions: We show a plasma-only genomic- and methyl-based assay to have sensitive and specific detection of MRD in stage II-III colon cancer. Serial measurement provides superior performance versus one-time measurement at Day 28 post-surgery and detects targets specific to early recurrence. Research Sponsor: None.

Median TTR based on single timepoint ctDNA detection in resected stage II/III colon cancer.

<table>
<thead>
<tr>
<th>Timing</th>
<th>ctDNA+ (n recurred/total)</th>
<th>ctDNA- (n recurred/total)</th>
<th>HR for Recurrence (95% CI)</th>
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<tr>
<td>28 days post-surgery</td>
<td>10/16 (62.5%)</td>
<td>6/24 (25%)</td>
<td>2.2 (0.96-5.3)</td>
</tr>
<tr>
<td>After chemotherapy</td>
<td>13/20 (65%)</td>
<td>7/23 (30.4%)</td>
<td>2.4 (1.2-4.9)</td>
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Analysis of immune-related genes (IRGs) and their potential role in sexual dimorphism in patients (pts) with metastatic colorectal cancer (mCRC). First Author: Pooja Mittal, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA.

Background: Sex-based disparities have been reported for mCRC both in incidence, males having higher incidence than females, and outcomes, younger females having better outcome than males of same age or older females. Tumor immunoevidence is hypothesized to have role in this sexual dimorphic pattern. Herein, we explored the role of gene expression (exp) and genetic variation of IRGs in pre-surgery-free (FS) and post-surgery survival (SS) in mCRC pts.

Methods: 21 IRGs with potential roles in CRC were identified from literature review and from accumulation of tumor gene exp with PFS and OS in mCRC. 451 pts of ctDNA+ pts were stratified into FS or SS based on pre-treatment samples from 114 non-recurred patients, sample specificity was 97.3% (95% CI 95.6-98.9%). Of these samples, the median age was 63 years old and the sex distribution was 55% males. MSH-2 was reported in 3.3% of samples. PIK3Ca included 25% E545 (Exon 9), 13% E542 (Exon 9), 5% Q546 (Exon 9), and 10% H1047 (Exon 20). PIK3Ca had increased median alterations (62.9% per sample vs 5% not detected (8 vs 5) and a significant increase in correlation with genes in the panel. Relevant clinical co-occurrences were APC (73.7% vs. 57.4%), BRAF (19.9% vs. 13.0%), EFRG (34.7% vs. 24.9%), ERBB2 (8.2% vs. 6.0%), and KRAS (62.6% vs. 41.2%). Additionally, PIK3Ca samples had higher median TMB scores (12.4 vs 9.8 mut/Mb), with >25% of PIK3Ca reporting a TMB score above the 80th percentile (8 mut/Mb). In a sub-analysis, there were significantly higher frequencies of PIK3Ca in 20 in BRAF V600E vs non-V600E BRAF mutations (p=0.0003) with no significant differences in exons 9 or 20 mutations in KRAS G12C vs. G13D.

Conclusions: Our study shows the frequency of PIK3Ca and distribution of exons 9 and 20 are similar to those found previously in the literature by Tan et al., 2022. Our results indicate a role of PIK3Ca having a potential role in prognosis and aggressive, and increased co-occurring alterations with notable increased in APC, BRAF, EFRG, ERBB2 and KRAS, which may suggest higher genomic instability. Our findings underscore the clinical significance of PIK3Ca in the context of CRC, emphasizing their role as key drug targets. Medications provide superior performance versus one-time measurement at Day 28 post-surgery and detects targets specific to early recurrence. Research Sponsor: None.

Prediction of postoperative recurrence by integrating preoperative ctDNA levels and tumor metastasis volume in patients (pts) with colorectal cancer (CRC) with resectable liver or lung metastasis. First Author: Hidekazu Oyoshi, Department of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan.

Background: In pts with CRC, the clinical usefulness of ctDNA testing after curative resection has been strongly suggested. Prognostic biomarkers are also needed for pts with resectable metastases to identify high-risk patients who may be spared unnecessary surgery or local ablation. We aimed to create a prediction model to estimate the risk of post-operative recurrence using an analytically validated multiomic ctDNA assay with radiographic imaging. Methods: A prospective study (UMIN000039205) included 645 pts with newly diagnosed or recurrent CRC with resectable liver/malign metastases within 3 months. The cutoff values for the ctDNA/volume model were 0.837 (liver) and 0.496 (lung) MTM/mL2. Among the pts with liver metastases, the median follow-up was 13.2 months (range: 0.7-30.9). The cutoff values for the ctDNA/volume model were calculated from the date of definitive surgical resection to first recurrence or death. Results: In this cohort of 110 pts with liver metastases and 24 with lung metastases, the median follow-up was 13.2 months (range: 0.7-30.9). The cutoff values for the ctDNA/volume model were 0.837 (liver) and 0.496 (lung) MTM/mL2. Among the pts with liver metastases, the high-risk group predicted by the ctDNA/volume model had a median DFS of 14.7 months (95% CI: 6.1–not reached) versus not reached (95% CI: not reached–not reached) in the low-risk group (HR = 3.6, P = 0.021). Among the pts with lung metastases, the median DFS was 2.9 months (95% CI: 2.1–not reached) in the high-risk group versus 21.8 months (95% CI: 21.8–not reached) in the low-risk group (HR = 2.10, P = 0.001). The high-risk group had a significantly higher cumulative recurrence at 6 months (17% and 67% in pts with liver and lung metastases, respectively) versus the low-risk group (p = 0.001). The high-risk group showed an overall death rate of 11% versus not reached (95% CI: not reached–not reached) in the low-risk group (p = 0.001). The high-risk group had a significantly higher cumulative recurrence at 6 months (17% and 67% in pts with liver and lung metastases, respectively) versus the low-risk group (p = 0.001). The high-risk group showed an overall death rate of 11% versus not reached (95% CI: not reached–not reached) in the low-risk group (p = 0.001).

Conclusions: The ctDNA/volume model was able to predict postoperative recurrence in CRC pts with liver and lung metastases. Ongoing and future studies will further optimize the model by incorporating other clinicopathologic factors and comparing with postoperative CRC recurrence. Research Sponsor: Grants-in-Aid for Scientific Research.

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Molecular and clinical characteristics of POLE/POLD1 alterations among patients with colorectal cancer. First Author: Masood Pasha Syed, University of Pittsburgh Medical Center Cancer Center, Pittsburgh, PA

Background: POLE and POLD1 alterations (DNA polymerase e and DNA polymerase i) are key biomarkers of immune response for patients with MSI colorectal cancers (CRC). The clinical and molecular characteristics of POLE/POLD1 alterations are not yet well defined across CRCs. In this study, we investigated the clinical/molecular features of POLE and POLD1 alterations and its association with MSI-H CRC. Methods: All the patients and mutation data were selected from the cbioPortal database (https://www.cbioportal.org). All nonsynonymous mutations including nonsense, frameshift, nonstop, splice site, and translation start site changes of POLE/POLD1 were considered. 17 patients were included in the analysis. 7179 data samples were obtained from 7179 patients. The clinic and the patients with MSI-H mutations were found to have recurrent MSI-H disease (co-existence) and only 1% of patients with POLE/POLD1 mutations had MSI CRC. MSI status was unknown for 1.7% of patients with POLE/POLD1 mutant CRC. The mean age for patients with POLE/POLD1 +/− with or without MSI-H disease was 67. POLE/POLD1 mutations were exceedingly more common in colon than rectum regardless of MSI-H status (85% vs 15% overall and 88% vs 12% in MSI-H subgroup). No difference was seen among genders for the distribution of POLE/POLD1 mutations. Conclusions: POLE/POLD1 mutations frequently co-exist with MSI-H CRC. Patients with MSS-CRC harboring POLE/POLD1 mutations represent a smaller subgroup of CRC (~1%). The incidence of POLE/POLD1 somatic mutations was more common among patients with colon cancer than those with rectal cancer. Research Sponsor: None.

Correlation between TP53, KRAS, SMAD4 and other mutations profile and neoadjuvant therapy efficacy and prognosis in locally advanced rectal cancer. First Author: Tomohiro Takeda, Department of Surgery, Asahikawa Medical University, Asahikawa, Japan

Background: Locally advanced rectal cancer presents a poor prognosis due to the risk of tumor recurrence and metastasis. Neoadjuvant chemoradiation therapy with mitomycin for locally advanced rectal cancer holds the potential for both local control and reduced distant recurrence, but identifying cases where its efficacy can be expected remains challenging. To explore predictive factors for the efficacy of NAC and prognosis in locally advanced rectal cancer. Methods: We examined 43 cases of locally advanced rectal cancer (CT3 or deeper, or cN3) that underwent primary tumor resection after NAC between January 2013 and June 2021. Genomic profiles were analyzed by extracting DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissues, including 24 pre-NAC biopsy samples and 39 surgical samples, excluding 4 cases with significant NAC response. Targeted sequencing was used for analysis, and mutations were considered positive if not classified as variants of unknown significance (VUS). Additionally, we examined 334 cases of locally advanced rectal cancer that underwent preoperative treatment using publicly available data in cbioPortal. Results: The median recurrence-free survival (RFS) was 1415 days (range: 97-2868) with 15 recurrences, and the median overall survival (OS) was 1,702 days (range: 97-2868) with 6 deaths (from the original disease, 1 from other cancers, and 1 of unknown cause). Among the 4 cases that showed histological response to NAC (AJCC Tumor Regression Grade 0-1), there was 1 recurrence, but no deaths occurred. RFS and OS in the CT3 group were favorable compared to those in the CT2-3 group, but the difference was not statistically significant (3-year RFS: 75% vs 65%, P=0.557; 3-year OS: 100% vs 92%, P=0.339). In targeted sequencing analysis, TP53 mutations were found in 32 cases, KRAS mutations in 19 cases, APC mutations in 14 cases, FBXW7 mutations in 5 cases, SMAD4 mutations in 4 cases, PIK3CA mutations in 2 cases, and NRAS mutations in 2 cases. Co-mutations were observed in 13 cases for TP53, 13 cases for KRAS, 8 cases for APC, and 5 cases for KRAS/APC. One case each of these co-mutations was observed in TRG0-1. From October 2020 to June 2023, 740 patients were screened for circulating molecular profiling. In the colorectal cohort (N=201), 198 (98.5%) patients had metastatic disease (cTRAS/BRAF wild-type, N=76 (38.4%); cTRAS, cBRAF mutant, N=106 (53.5%); and cBRAF wild-type, cTRAS mutant, N=16 (8.1%)). The optimal threshold for cTRAS/BRAF was 5% (C-index 0.67, 95% CI 0.62–0.73; P<0.0001). Among patients with cTRAS mutant MCRG, 43 (40.6%) were cTRAS-mutant- Low (VAF<5%) and 63 (59.4%) were cTRAS-mutant-High (VAF>5%). Median follow-up was 18.5 months (95% CI 15.3-34.5). There was a significant increase in the risk of death for RAS-mutated-High compared to RAS-mutated-Low (HR 2.81, 95% CI 1.70-4.63; P=0.001). Patients with RAS-mutated-Low variants had the same prognosis that BRAF mutant profile (HR 1.70, 95% CI 1.00-2.90). The factors associated with RAS-mutant-High profile were: BMB-High, TMB-High, and cBRAF G605E variants. MAPK and mTOR pathway mutations were frequent in patients with cTRAS-mutant-High. We observed a transient decrease of VAF in secondary-line setting. Conclusions: The circulating VAF of RAS genes enables to split RAS-mutant-Low (favorable prognosis similar to RAS/ BRAF wild-type) from RAS-mutant-High (poorer prognosis similar to BRAF mutant) metastatic colorectal cancer. These results provide further insights into prognostic and therapeutic strategies in patients with RAS mutant metastatic colorectal cancer. Research Sponsor: None.

Identification of MAPK and mTOR pathway alterations in HER2-amplified colorectal cancer. First Author: Svea Cheng, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Human epidermal growth factor receptor 2 (HER2) amplification is now a highly actionable alteration for patients with colorectal cancer (CRC) with distinct combination therapies. Recent studies have shown that oncogenic KRAS, BRAF, and PIK3CA mutations, may serve as biomarkers of response to HER-directed treatments such as Trastuzumab and Tucatinib/Pertuzumab. In this study, we investigated the incidence of MAP kinase and mTOR pathway alterations in patients with HER2-amplified CRC. Methods: The cbioPortal for Cancer Genomics was utilized to collect data and graphics on HER2 amplification in CRC. cbioPortal was queried to select 21 published studies that contain CRC specimens (assessed April 2023). Clinical, specimen, copy number alteration (CNA), and somatic mutation data of each study were downloaded and aggregated across all studies, followed by filtering, standardization, and harmonization to generate ~30 analysis-ready fields encompassing demographic variables, HER2 amplification, and KRAS/NRAS/PIK3CA/BRAF mutations. Results: Among a pool of 4822 CRC patients with known gender, 44.4% (2139) were female and 55.6% (2683) were male. The incidence of HER2 amplification in the overall cohort was 2.6% (123/4822) and was noted to be higher in males (3.1%, 82/2683) than in females (1.9%, 41/2139). The incidence of HER2 amplification was highest in Asian CRC patients (3.9%, 9/228), followed by Black CRC patients (3.0%, 9/298), and then Caucasian CRC patients (2.7%, 57/2118). Rates of HER2 amplification were similar in the colon and rectum at 2.6% (61/2360 and 26/1015, respectively). After analyzing rates of concurrent MAPK and mTOR pathway mutations in patients with HER2-amplified CRC, NRAS mutations were noted to be significantly lower in HER2-amplified colon cancer (2.7%, 7/161), but were less common in HER2-amplified rectal cancer (7.7%, 2/ 26). PIK3CA mutations were also common, with an incidence of 13.1% (8/61) in HER2-amplified colon cancer and 7.7% (2/26) in HER2-amplified rectal cancer. NRAS mutations correlated with the low rates of HER2-amplified colon cancer, and at 3.3% (2/61) and 3.8% (1/26) respectively. No BRAF mutations were reported in either disease group. Conclusions: In this study, we identified that MAPK and mTOR pathway alterations are relatively common among patients with HER2-amplified CRC. These somatic events appear to be more common in HER2-amplified colon cancer than rectal cancer. Next generation based molecular profiling is recommended to identify potential resistance mechanisms before initiation of HER2-directed therapy. Research Sponsor: None.
Myostatin/activin pathway gene expression and single nucleotide polymorphisms (SNPs) in metastatic colorectal cancer (mCRC). First Author: Karam Ashrafi, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

**Background:** Cancer cachexia leads to reduced overall survival (OS) in mCRC. Novel strategies targeting the myostatin/activin pathway can reverse cachexia. Here we investigate the effect of myostatin/activin pathway gene expression and SNPs in mCRC patients (pts).

**Methods:** Blood samples were obtained from 311 pts treated with 1st-line TRIBE for CRC metastases. Genotyping for 200 single nucleotide polymorphisms (SNPs) was performed on Illumina Infinium II CHIP. The association between clinical outcomes and genetic variants was analyzed by Cox proportional hazards regression for OS and progression-free survival (PFS), using Kaplan-Meier estimates and log-rank analysis. The association of gene expression with clinical outcomes was analyzed using Cox regression, adjusting for multiple hypothesis testing by Benjamini-Hochberg.

**Results:** SNPs were associated with clinical outcomes. Among the genes investigated, **ACVR1B** was associated with longer PFS (L/M/H, 9.5 vs. 7.6 vs. 11.2 mo; UV \( P = .035 \)). Genes associated with shorter OS included **CDK8** and **CDK6**, with hazard ratios of 0.47 (95% CI 0.22-1.02) and 0.54 (95% CI 0.30-0.95), respectively. The association of gene expression with clinical outcomes was consistent across primary and metastatic sites.

**Conclusions:** The results suggest that genetic variants and gene expression may be useful biomarkers for predicting clinical outcomes in mCRC. Further studies are needed to validate these findings and to elucidate the role of the myostatin/activin pathway in cancer cachexia.

**Poster Session**

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Incidence and genomic characteristics of gene fusions in a large Chinese colorectal cancer cohort. First Author: Furong Kou, Key Laboratory of Carcino- genomics and Translational Research (Ministry of Education), Department of Medicine, Peking University Cancer Hospital & Institute, Beijing, China

Background: Gene fusion is rare in colorectal cancer (CRC). With the advent of fusion-targeted therapeutics, such as entrectinib for NTRK fusion and selenosertib for RYR2 fusion, the identification of gene fusions holds clinical significance. Reports providing a comprehensive description of fusions in CRC are limited, and understanding the molecular characteristics of CRC with fusions will contribute to efficient fusion screening. Here, we investigated the incidence and genomic features of gene fusions in a Chinese CRC population.

Methods: We systematically analyzed next-generation sequencing results of tumors from 5534 CRC patients between January 2020 and August 2023. The sequencing panel covers 769 cancer-related genes and can detect fusions, single nucleotide variants and indels, and microsatellite instability status (MSI).

Statistical significance was determined using chi-square test. Results: Overall, the median age of 62 patients was 62 years (inter-quartile range [IQR] = 53-70), and 40% were female. Gene fusions were detected in 4.24% (242/5534) of all the patients. The incidence is 0.98% (54/5534) if only reported clinically actionable fusions are considered. The median age of the 242 fusion-positive patients was 64 years (IQR 54-70), and 43% were female. The most highly detected potentially actionable gene fusions were NTRK1 (0.89%) and FGFR (0.81%), accounting for 39% of the fusion-positive patients. The other fusion genes were ERBB2 (0.52%), RET (0.38%), BRAF (0.31%), EGFR (0.27%), ALK (0.22%), MET (0.09%) and RUS1 (0.07%). Consistent with previous reports, patients with MSI were more likely to have fusions compared with those with microsatellite stability (MSS) or MSI-Low (9.9% vs 4.0%, p < 0.001). Besides, RAS or BRAF mutated patients accounted for 59% of the cohort, of whom 2.5% (83/3273) had fusions detected, while 7.0% (159/2261) of the RAS and BRAF wildtype patients had positive fusions (p < 0.001). Moreover, 404 (7.3%) patients had RNF43 splice or truncating mutations, and gene fusions were detected in 4.4% of the Chinese CRC population and tended to occur in patients with wildtype RAS/BRAF, MSI-H, or RNF43 mutations. Combining the mutational status of RAS, BRAF, and RNF43 along with MSI status can improve the fusion detection rate and help select candidates for fusion testing and targeted therapy. Research Sponsor: Foundation Medicine, Inc.

Impact of acquired RAS, BRAF and PIK3CA mutation at 8 weeks on the efficacy of anti-EGFR monoclonal antibodies in metastatic colorectal cancer. First Author: Takeshi Yamada, Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo, Japan

Background: Recent studies indicate that the emergence of RAS/BRAF mutation sometimes occurs during initial anti-EGFR monoclonal antibody (mAb)-based treatment in metastatic colorectal cancer (mCRC). However, limited data was available regarding the timing and frequency of the emergence of RAS/BRAF mutation, and its impact on the efficacy of anti-EGFR mAb. With this background, we conducted an observational study to monitor RAS, BRAF, and PIK3CA mutation status by ctDNA in RAS/BRAF wt mCRC.

Methods: RAS-trace is a pilot study to monitor RAS, BRAF, and PIK3CA mutation status by ctDNA, using NGS-based Plasma-Safe-SeqS technology for RAS/BRAF wt (diagnosed from tissue samples) mCRC treated with anti-EGFR mAb as a first-line chemotherapy. ctDNA-RAS/BRAF/PIK3CA status evaluated at baseline, 8, 16, 20, 24, 36, 48 weeks and disease progression. The primary endpoint was the time to the acquired RAS mutations. The results of ctDNA at baseline and 8 weeks are presented. Results: Forty-two patients were enrolled, and 40 and 39 were used in the analysis of ctDNA at baseline and 8 weeks, respectively. All patients received mFOLFOX6 plus cetuximab (N=32) or panitumumab (N=8). At baseline, RAS, BRAF, and PIK3CA mutations were detected in 3, 3, and 1 of the 40 patients, respectively. One patient had both KRAS and BRAF mutations. Baseline ctDNA mutations were not associated with the presence of liver metastases, tumor sidedness, early tumor shrinkage, depth of response or skin rash ≥Grade 2. At 8 weeks, RAS, BRAF, and PIK3CA mutations were detected in 3, 2, and 0 among the 39 patients, respectively. One patient had both KRAS and BRAF mutations. ctDNA mutations at 8 weeks were not associated with the presence of liver metastases, tumor sidedness, or early tumor shrinkage. Patients with ≥Grade 2 skin rash were associated with depth of response and had a tendency of skin rashes ≥Grade 2 (Table). Conclusions: Baseline RAS/BRAF/PIK3CA mutations at 8 weeks may be related to the response of anti-EGFR mAb. The association of ctDNA status with survival outcomes will be presented in 2025. Clinical trial information: JRCT1050210160. Research Sponsor: Sysmex Corporation.

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Tissue factor: A link between metastatic colorectal cancer and thrombosis in patients in the CALGB (Alliance)/SWOG 80405 trial. First Author: Sandra Alagaez, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA

Background: Tissue factor (TF) is a transmembrane protein that plays a crucial role in thrombosis. TF is elevated in various types of cancer, including colorectal cancer (CRC) and is associated with more aggressive disease and poor prognosis. The aim of this study was to evaluate TF expression in patients (pts) with metastatic CRC (mCRC) enrolled in the CALGB (Alliance)/SWOG 80405 clinical trial. Understanding the relationship between TF expression and CRC patient outcomes is important in the context of acquired resistance to antiangiogenic therapy (AAT) and treatment for CRC. TF expression might be associated with the presence of coagulation in cancer patients and represent a potential biomarker for disease progression.

Methods: 433 pts with mCRC treated with bevacizumab (Bev, n = 226) or cetuximab (Cet, n = 207) in combination with first-line chemotherapy in CALGB/SWOG 80405 were included in the analysis. TF RNA was isolated from FFPE tumor samples and sequenced on the HiSeq 2500 (Illumina). Overall survival (OS) and progression-free survival (PFS) were compared between groups of pts categorized by tertiles of TF expression: high (H), medium (M) and low (L). Sensitivity analyses were conducted after accounting for covariates.

Logrank P-values describe differences without adjustment for pt characteristics. Transcriptome-wide gene association analysis was performed using linear regression, adjusting for age, sex, ethnicity, ECOS PS location, number of metastases, KRAS status, treatment with FOLFOX or FOLFIRI, and the first 3 principal components from the RNA-seq data. TF expression was correlated with the top 110 TF-associated genes. Results: TF expression is associated with genes related to maintenance of epithelium, cell adhesion, and migration, immunoregulatory cytokine production, and metabolic, HER2, and MAP/kinase pathways. TF-L showed significantly longer median PFS (13.2 vs 10.9 vs 8.2 months, p = 0.0014) and OS (33.4 vs 30.9 vs 22.4 months, p = 0.0044). Pts with liver metastases and TF-H had worse PFS (9.2 vs 12.9 vs 10.5 months, p = 0.019) and OS (23.6 vs 21.9 vs 19.7 months, p = 0.016). The combined results suggest that TF-L tumors with liver metastases have improved prognosis compared to pts with TF+H and may benefit from FOLFIRI and Bev-based treatment. Findings provide rationale for further evaluation of TF as a predictive biomarker and potential therapeutic target in CRC.

Conclusions: TF expression is associated with several CRC-related genes and may be a potential biomarker for disease progression. TF-L may be associated with a better prognosis compared to TF+H. Further research is needed to validate these findings and explore the clinical implications of TF expression in CRC.
Utilizing quantitative pathologic analysis of digitized images of rectal cancer (RC) to predict response to neoadjuvant therapy (NAT). First Author: Daniel Wolfson, Department of Hematology/Oncology, Mayo Clinic Arizona, Phoenix, AZ.

Background: We developed and validated a quantitative segmentation algorithm (QuantCRC) to predict disease recurrence in stage I-III colorectal cancer patients (pts) based on the analysis of digitized hematoxylin and eosin (H&E) stained pathology slides. In this study, we aim to determine if QuantCRC analysis on pre-treated RC biopsies can predict pathologic complete response (pCR) after neoadjuvant therapy (TNT), and neoadjuvant therapy (CRT) and others.

Methods: Stage II-IV RC pts treated with curative intent modalities between 2005-2023 at Mayo Clinic and University of Pittsburgh were evaluated. Eligible pts had pre and post-treatment tissue available for analysis. Clinical characteristics, treatment, and outcome data were extracted from the medical record. QuantCRC extracted 15 features: %tumor, %stroma, tumor:stroma ratio, %TB/PDC, %mucin, %necrosis, %malignant (stromal region), tumor infiltrating lymphocytes (TILs) per cm2 of a tumor, %immature stroma (tumor bed), %inflammatory stroma (tumor bed), %mature stroma (tumor bed), %fibroblastic (stromal region), %stroma (fibroblastic region), and %stroma (stromal region). The associations between the QuantCRC features and pCR were evaluated using Wilcoxon rank-sum tests and logistic regression models while adjusting for primary tumor location and NAT.

Results: The identified 282 pts had the following demographics: median age 60, 59% male, 57% distant tumor, 42% TNT. Pts who achieved pCR had smaller pre-treatment tumors (p=0.03), higher TILs, and lower %immature stroma (Table 1). After multivariable adjustment, higher TILs and lower %immature stroma (stroma bed) remain to be significantly associated with a higher likelihood of pCR. A higher % mature stroma (%stroma tumor bed) were also identified, in multivariable models, to be associated with a higher rate of pCR. NAT protocol and tumor location (proximal vs. distal) were not associated with pCR. Conclusions: The ability to integrate pathologic features with AI may allow for personalized treatment. Using this technology, we recognize that patients who harbor a more mature stroma architecture and inflammatory tumor predisposition, are more likely to achieve CR to conventional NAT. These pathologic features are not currently incorporated into risk stratification in RC. Additional validation and integration into current risk stratification methods is warranted.

OS distribution depending on cohort and mutational status.

<table>
<thead>
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<th>Mutation status</th>
<th>Cohort A</th>
<th>Cohort B</th>
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<tr>
<td>N (%)</td>
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<td>N (%)</td>
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<td>KRAS G12</td>
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<td>KRAS G13</td>
<td>8 (8) 4.1 3.2 NR 21 (10) 7.0 4.9 NR</td>
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<td>RAS/RAF-WT</td>
<td>42 (42) 11.8 7.9 NR 63 (31) 13.9 10.6 NR</td>
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OS distribution depending on cohort and mutational status.
Association of pathologic nodal status with minimal residual disease after neoadjuvant treatment and resection of locally advanced rectal cancer. First Author: Abhinheet Upadhye, Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Studies have shown that minimal residual disease (MRD) identified by detection of circulating tumor DNA (ctDNA) is associated with recurrence after surgical resection of colorectal cancer. Though multiple trials are evaluating the use of ctDNA to guide adjuvant therapy, data on the utility of ctDNA after neoadjuvant therapy is limited. In this study, we evaluated the associations between ctDNA and recurrence after neoadjuvant treatment and resection of rectal cancer (LARC). Methods: Consecutive patients with primary rectal cancer treated with neoadjuvant systemic therapy and/or chemoradiotherapy followed by resection between 12/2020-4/2023 were identified. Patients were tested for ctDNA via the MD Anderson INTERCEPT platform using a high-sensitivity patient informed assay. Patient metadata or a first ctDNA test more than 3 months after resection were excluded. MRI-determined stage, extramural vascular invasion (meSMVI), pelvic sidewall adenopathy (PSW), pathologic lympho-vascular invasion (LVI), perineural invasion (PNI) and tumor regression grade (TRG) were collected. Associations between these factors and ctDNA status were analyzed with Fisher’s exact test. Recurrence free survival (RFS) was analyzed with the log-rank test.

Results: Sixty-seven patients (3 treated with chemoradiation alone, 15 with systemic therapy alone and 49 with total neoadjuvant therapy) were identified. Positive ctDNA was identified in 6 (8.9%) within 3 months after resection, all of whom received total neoadjuvant therapy, and 3/6 recurred within 12 months. Clinical T status (p=0.146), N status (p=0.842), meSMVI (p=0.475) and PSW (p=0.316) were not associated with MRD. TRG was not associated with MRD (TRCGT-1: 4% vs TRGC2-3: 13%, p=0.547). Pathologic N status was associated with MRD (ypN0: 4.4% vs ypN+: 18%, p=0.049). MRD was associated with a median RFS of 3.2 months (HR 39.2, 95% CI: 4.1-380, p=0.0015). 1-year RFS was 98% for patients without MRD. Conclusions: Minimal residual disease after multi-modal treatment of LARC is associated with metastatic recurrence. The patient informed MRD assay appears both sensitive and specific for detection of relapse. Advanced clinical stage and high-risk radiologic features were not associated with MRD, while post-treatment pathologic N status was. Given the high relapse rate for MRD+ patients, MRD detection after resection warrants additional investigation for metastases and/or enrollment on MRD treatment clinical trials. Methods to predict MRD prior to resection are urgently needed. Research Sponsor: None.

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Tumor genomics and sidedness to predict outcomes in metastatic colorectal cancer (mCRC). First Author: Patrick M Boland, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Tumor sidedness is a prognostic factor and predictive parameter for EGFR monoclonal antibody (mAb) treatment in mCRC. Sidedness is believed to be a surrogate for genotype. This study aimed to evaluate genomics versus sidedness for prediction for the development and progression of cancer in young onset (under age 50) colorectal cancer patients. Methods: We included patients (pts) with microsatellite stable mCRC tested by Foundation Medicine tissue comprehensive genomic profiling assay. Patient data was obtained by the US-based de-identified Flatiron Health-Foundation Medicine real-world clinical database (FH-FMI CGDB), originating from approximately 280 US cancer clinics (1/2011-3/2023). Genomic alterations (GA) in 324 genes were compared between right and left side tumors using Fisher’s exact test, adjusted for multiple comparisons. Real-world progression-free survival (pPFS) and overall survival (pOS) were compared by univariable (categorical) and multivariable models (Cox proportional hazards model) adjusted for both sidedness and genotype. Results: From 3845mCRC pts (2584 left and 1261 right) were included. Genes in APC, TP53, ARID1A, and FBXW7 were more prevalent in left side, while GA in AMER1A, PIK3CA, APC, CTNNB1, and CTNNB1 were more prevalent in right side. RAS pathway was associated with sidedness. Conclusion: Sidedness is a useful tool in clinical practice when no molecular data is available. However, the current study cannot differentiate if sidedness and genomics are independent or if they are capturing the same molecular changes.
Identification of somatic alterations associated with brain metastases from a colorectal origin. First Author: James S. Strong, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Colorectal brain metastases (cBM) confer a devastating prognosis with survival of less than 13 months. Identifying genomic signatures to predict and guide treatment for these patients would be a valuable adjunct. This study evaluated genomic and clinicopathological features specific to cBM. Methods: cBM patients from the MSK-MET cohort were evaluated in comparison to other colorectal cancer patients with extracranial metastases. Genomic features and genomic alterations were analyzed with MSK-IMPACT, a targeted DNA sequencing panel for solid tumors and matched blood specimens. We considered mutations, copy number alterations, and fusions. Analyses of genomic features were restricted to microsatellite stable (MSS) patients. q-values were computed using Benjamini-Hochberg correction to account for multiple hypothesis testing. Patient record review identified patients with sequenced matched samples from the primary colorectal tumor and the brain metastases, which were then examined for loss and gain of assessed genetic alterations. Results: Of 130 patients with cBM identified from the cohort, 20 samples were from brain metastases, 52 from the primary CRC, and 58 from other metastatic sites. Average time to diagnosis of cBM was 3.5 years after primary colorectal cancer diagnosis and average time to death was 10 months after cBM diagnosis. Compared to the 3,383 cOM patients, cBM patients had significantly higher rates of both MSS CRC primaries (p < 0.001, 122/130 cBM were MSS vs. 0.038,3,382 cOM) and primaries that originated in the rectum (p < 0.002, with 38/130 cBM primaries from the rectum vs. 695/3,388 cM rectal primaries). Somatic alterations in the KRAS, BRCAl, CDKN2A and ERCC5 genes were significantly more frequent in patients with cBM compared to cOM patients (all p < 0.001) (Table 1). Of the 9 patients who had matched primary and metastatic brain tissue sequenced, KRAS alterations were shared between the primary and metastatic brain in 2/9, EBRB3 and ERCC5 in 2/9, p53 in 6/9, and APC in 6/9 patients. In addition, newly acquired private alterations found only in the brain metastasis samples matched of patients included PIK3R1, ARID5B, NOTCH4, CYLD, and SMAD4. Conclusions: We identify new genomic and clinical factors in cBM patients, including somatic alterations in potentially clinically actionable targets. To further explore potential clinical utility, these findings require validation in an independent cBM clinicogenomic database. Research Sponsor: None.

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Serum angiopoietin-like protein 2 level in patients who received bevacizumab-containing chemotherapy for metastatic colorectal cancer. First Author: Jung Hoon Kim, Pusan National University Yangsan Hospital, Yangsan-Si, South Korea

Background: Anti-angiogenic agents are important for treating patients with advanced colorectal adenocarcinoma, however, their efficacy is not long-lasting and survival benefits are modest. Reliable biomarkers and novel targets for angiogenesis are still required in this era. Angiopoietin-like protein 2 (AGLP-2) is an emerging biomarker for angiogenesis in cardiovascular disease, but its role in the oncology area is yet to be elucidated. Methods: Serum samples from patients with advanced colorectal carcinoma treated with bevacizumab-containing chemotherapy were retrospectively studied. Blood samples at baseline and at disease progression of the first line systemic therapy were selected. Serum angiopoietin-like protein 2 (AGLP-2) concentrations were measured using ELISA kit, serial changes, and the relationship with progression-free survival and overall survival were analyzed. Results: 68 patients were enrolled. Their median age was 66 years old (range, 38-82), and 14 (20.6%) patients had metastatic lesions at 3 or 4 organs. The median serum AGLP-2 levels at baseline and at disease progression (PD) were 41,618 pg/mL (95% confidence interval (CI) 34,560-40,713), and 49,706 pg/mL (95% CI 39,853-49,017), respectively. There was a tendency of difference between AGLP-2 levels at baseline and at PD (p=0.057). Patients whose baseline AGLP-2 levels with 40,000 pg/mL or above showed relatively shorter overall survival (median 31.4 months with 95% CI, 14.4-38.6) compared with patients with serum AGLP-2 level below 40,000 pg/mL at baseline (median 38.6 months with 95% CI, 23.6-127.3), but not statistically significant (p=0.9896). There was no survival difference observed according to serum AGLP-2 levels at disease progression on the first line bevacizumab-containing chemotherapy. Conclusions: Serum angiopoietin-like protein-2 has potential as a new target for novel anti-angiogenic therapy in metastatic colorectal cancer. Research Sponsor: None.

211 Poster Session

BRAF variants and oncogenic fusions to define sporadic MMR-deficient colorectal cancer subtypes. First Author: Sameer Abdeltawwab, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Mismatch-repair deficient (MMRd) colorectal cancers (CRC) are rare tumors exclusively sensitive to immunotherapy. The molecular events that initiate and sustain MMRd CRCs remain controversial. The majority of sporadic MMRd CRCs exhibit MSI-H phenotypes. Clinopathological features and genomic alterations were analyzed with MSK-IMPACT, a targeted DNA sequencing panel for solid tumors and matched blood specimens. We considered mutations, copy number alterations, and fusions. Analyses of genomic features were restricted to microsatellite stable (MSS) patients. q-values were computed using Benjamini-Hochberg correction to account for multiple hypothesis testing. We analyzed 1,656 longitudinal plasma samples from 257 rectal cancer pts (clinical stages I: 7%; II: 23%; III: 65%; IV: 5%). A personalized, tumor-informed assay [complete response: 8% (ctDNA+ vs. 51% (ctDNA-), p=0.0017]. Of the 87 pts with post-NAT tp was available for 87 pts, of whom 29.9% (26/87) were ctDNA+ and were less likely to achieve a clinical response to NAT (DFS; NAT: HR=13, 95% CI: 5.8-31, p=0.0001; no NAT: HR=12, 95% CI: 3.9-3957, p<0.0001). In an independent cBM clinicogenomic dataset. Research Sponsor: None.

212 Poster Session

Prognostic value of circulating tumor DNA (ctDNA) testing in patients (pts) with rectal cancer after neoadjuvant therapy (NAT) and surgery. First Author: Sakti Chakrabarti, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Cleveland, OH

Background: ctDNA is a highly prognostic biomarker for pts with CRC. However, the value of ctDNA as a biomarker for decision-making is not fully elucidated. The association of post-NAT and post-surgical ctDNA status with outcomes in rectal cancer pts. Methods: We analyzed 1,656 longitudinal plasma samples from 257 rectal cancer pts (clinical stages I: 7%; II: 23%; III: 65%; IV: 5%). A personalized, tumor-informed assay (Signatera, Natera, Inc.) was used for ctDNA detection and quantification. In this cohort, 169 (clinical stages I: 7%; II: 23%; III: 65%; IV: 5%). A personalized, tumor-informed assay (Signatera, Natera, Inc.) was used for ctDNA detection and quantification. In this cohort, 169 pts had nonoperative management (NOM) after NAT. NAT included total neoadjuvant therapy (NOM cohort). Event-free survival (EFS) was defined as the interval from end of NAT to the date of clinical progression (NOM cohort). Disease-free survival (DFS) was defined as the interval from surgery to radiological recurrence. Results: The median follow-up was 619 (0-2,535) days. Pre-treatment ctDNA results were available for 50/257 pts; 94% (47/50) of whom were ctDNA+. Post-NAT tp was available for 87 pts, of whom 29.9% (26/87) were ctDNA+ and were less likely to achieve a clinical response to NAT (DFS; NAT: HR=13, 95% CI: 5.8-31, p=0.0001; no NAT: HR=12, 95% CI: 3.9-3957, p<0.0001). In an independent cBM clinicogenomic dataset. Research Sponsor: None.
Correlation of exploration of immune profile and genomic with microsatellite stable/stable tumor mutation burden-low colorectal cancer. First Author: Hassan Mohamad Abushukair, Jordan University of Science and Technology, Irbid, Jordan

**Background:** Microsatellite stable/tumor mutation burden-low (MSS/TMB-L) tumors, represent the majority of colorectal cancer (CRC) patients and derive limited benefit from immune checkpoint inhibitors (ICI). Given the vast heterogeneity of this population, some patients may be candidates for ICI. Herein, we study the tumor immune microenvironment (TIME) and genomic correlates associated with favorable immune response in MSS/TMB-L CRC patients. Methods: The Cancer Genome Atlas (TCGA) and the Colorectal Adenocarcinoma (TCGA-COAD) cohort (n = 594), MSS patients (MSI Mantis score < 0.4) with TMB-L (<10 mutations/megabase) were identified. The CIBERSORT algorithm was used to calculate the fraction of 22 immune cells using RNA-seq data. Relevant immune expression signatures from the CRI Atlas were used to assess TIME profiles. An antitumor immune activity (AIA) score was constructed using CD8+ T cells, T regulatory cells, and M1 & M2 macrophage fractions. Enriched mutations in MSS/TMB-L patients with favorable antitumor immune scores were identified and used to stratify patients into favorable and unfavorable immune profiles (FIP / UFP). Comparisons were made using the Mann-Whitney U T-test and Fisher’s exact test. Results: We identified 430 (72.4%) MSS/TMB-L patients among the TCGA-COAD cohort. The AIA score ranged from -0.44 to 0.62 (higher scores denote favorable AIA activity). The majority of patients (77%) had scores < 0. Top enriched mutated genes associated with higher scores included HMGB2, BSF2, JFLNR1, SLC30A2, WDR48, ZNF329, HCF1, PARD6B, ENAM, ASCC1, CDC6886, CKMR1, IL21, KHL11, and OPOP. Patients harboring a mutation in one or more of these 15 genes were categorized in the FIP group (n=50, 11.6%) and patients with no mutations were categorized in the UFP group (n=360, 88.4%). The FIP group had significantly (p < 0.05) higher levels of TMB, CD8+ T cells, activated NK cells, M1 macrophages, immunogenic SNV mutations, and cytoytic activity while patients with UFP had higher levels of p53 mutations, neutrophils, and a trend for higher regulatory T cells and TH17 cells. Gene set enrichment analysis showed upregulation of T cell proliferation, interferon signaling, and Fc receptor anemia pathway in FIP. Compared to UFP, FIP patients had a trend for better disease-specific survival after adjustment for CC subtype (colon vs. rectum) and age (HR: 0.26, 95% CI: 0.10-0.69, p = 0.0066). Conclusions: Findings from this analysis highlight a subset of MSS/TMB-L CRC patients, with features of favorable anti-tumor immune response and unique mutation profile, that might derive benefit from immunotherapy. Further investigation is underway to further explore the genomic correlates in this subset of patients. Research Sponsor: None.

Surveillance of resected metastatic colorectal cancer utilizing circulating DNA. First Author: Nikolas Naleid, Department of Internal Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH

**Background:** There is limited data to guide surveillance in patients with metastatic colorectal cancer (CRC) who have had curative resection using circulating tumor DNA (ctDNA) in addition to labs and imaging studies. Minimal residual disease (MRD) assays utilize circulating tumor DNA (ctDNA) for the purposes of monitoring for early recurrence and predicting therapeutic response. In this study, we aim to investigate the utility of ctDNA monitoring in the setting of resected metastatic CRC. Methods: Patients were identified through retrospective search at a tertiary care and several satellite settings to identify patients with metastatic CRC who had undergone curative resection and later had ctDNA monitoring (using Signatera assay). IRB approval was obtained for the study. We recorded demographic information (sex, race, age at diagnosis), disease characteristics (stage at diagnosis, site of primary cancer, site of metastasis), treatment regimens, clinical outcomes (recurrence, survival) and follow-up data. Our primary outcome was to evaluate the rate of recurrence in patients with metastatic CRC who had curative resection in two different population, ctDNA positive or ctDNA negative, post-surgery. Results: We identified 35 patients with a median age of 55 years (range 31 – 82) at the time of metastatic diagnosis. In this study cohort, 23 (66%) were female; 23 (66%) were white, and 10 (29%) were African American. 22 (63%) patients had left-sided primary tumors and the remaining (47%) had right-sided primary tumors. At the time of presentation, 23 (66%) patients had synchronous metastases and 12 (34%) developed metachronous metastases. ctDNA positivity was reported in 21 (60%) pts post-curative therapy. Median time from curative therapy to ctDNA positivity was 62 days. 22 (66%) patients developed disease recurrence after curative resection. Median time to recurrence after ctDNA test was first positive was 6.6 months. Among 21 patients in ctDNA positive group, 19 (86%) developed recurrences and among 14 ctDNA negative patients, only 3 (21%) developed recurrences (p-value <0.01). Recurrence free survival was significantly shorter in patients who were ctDNA positive post surgery (Median RFS: 7.17 months, 95% CI: 4.4-18.0 months) compared to those who were ctDNA negative. Conclusions: In patients with metastatic CRC who underwent curative resection ctDNA may have utility in predicting disease recurrence at both academic and community sites. Larger studies are needed for validation of ctDNA as an adjunct test for surveillance in broader population. Research Sponsor: None.

Impact of somatic genomic alterations in patients with metastatic colorectal cancer in a minority-rich academic medical center. First Author: Jessica Jang, Albert Einstein College of Medicine, Bronx, NY

**Background:** Genomic alterations in metastatic colorectal cancer (mCRC) play a pivotal role in the clinical manifestations of the disease. Mutations have been associated with the location of mCRC, tumor histology, and metastatic sites. This retrospective study sought to explore the relationship between the genomic profile and clinical phenotype in a distinct patient population predominantly comprised of Hispanic and Black patients with mCRC. Methods: Patients with mCRC with available next-generation sequencing (NGS) treated at Montefiore Einstein Comprehensive Cancer Center (MECCC) who underwent curative intent were included. Molecular testing was collected from: Perthera, Guardant, Caris, and Foundation One. The following parameters were collected: race, ethnicity, age of CRC diagnosis, age of metastatic diagnosis, metastatic sites, NGS profile, tumor location, and lines of treatment. Mutations were categorized into one of eight distinct pathways: cell cycle, MAP Kinase, WNT, homologous recombination, DNA damage repair, epigenetic modifications, transcription, & cell death. The primary endpoint was to examine the relationship between individual genetic alterations or any of these eight pathways and the clinical parameters. Results: 169 patients with microsatellite stable (MSS) mCRC were included (median age at diagnosis 59 years, 42% Hispanic, 38% Black). 148 distinct genetic alterations were discovered across our population, of which roughly half fit into one of eight clinical pathways. In concordance with previously published data, we found a significant association between PTEN and right-sided tumors (38% mutated in right-sided vs. 16% mutated in left-sided, p <0.001). Cell cycle pathway mutations and SMAD4 mutations were associated with an earlier age of both primary CRC (p< 0.01 & p=0.42, respectively) and metastatic diagnosis (p<0.01 & p=0.013, respectively). CDK6 mutations were associated with atypical sites of metastases (p=0.045). Conclusions: This analysis sought to deepen the understanding of how genomic alterations impacted the clinical phenotype in our population of mCRC patients. We identified previously undescribed associations between mutations in the cell cycle pathway and SMAD4 variants. As molecular sequencing in CRC continues to advance, these relationships may be further elucidated, which can potentially help guide treatment and identify high-risk patients. Research Sponsor: None.

“Choosing wisely” in oncology: The example of surveillance positron emission tomography-computed tomography (PET-CT) for patients with colorectal cancer (CRC) treated with curative intent. First Author: Roi Tscherenkovich, Davidoff Cancer Center Rabin Medical Center, Petah Tikva, Israel

**Background:** Healthcare overuse is a major challenge for healthcare systems. Professional guidelines, such as Choosing Wisely, have been put in place to mitigate specific areas of overuse. We examined whether the rate of unwarranted PET-CT in CRC patients treated with curative intent was successfully reduced following the adoption of Choosing Wisely. Methods: We used the large Clalit Health Services dataset in Israel to identify patients with CRC who received adjuvant chemotherapy for localized disease between January 2017- December 2021. We then examined the number of PETCTs performed for each patient. Results: 1799 patients were included in our study (Table). We distinguished localized from metastatic cases based on specific drugs administered or not administered during the follow-up period (i.e. biologics). For the entire cohort, the median number of PETCTs performed per patient per year study period was 3. 364 (20.2%) patients underwent a single PETCT, 946 (52.6%) patients underwent ≥2 PETCTs, and 25 patients underwent ≥10 PETCTs. Assuming a single PETCT is considered “guideline concordant” during diagnosis and treatment of localized CRC, 52.6% (946/1799) of patients in our cohort underwent “guideline discordant” PETCT scans. Conclusions: Despite professional guidelines recommending against routine PETCT to monitor for recurrence following curative-intent treatment of CRC, there remains a large volume of “guideline-discordant” PETCTs in this space. Professional guidelines such as “Choosing Wisely” have largely failed to prevent this example of healthcare overuse. Research Sponsor: None.

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Investigating the association of WNT pathway dysregulation and young-onset colorectal cancer. First Author: Morgan Ferrer, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Colorectal cancer (CRC) is the third most common cancer in the United States with studies showing increasing incidence of Young-Onset CRC, defined as cases occurring in individuals 50 years old or younger. Separately, the WNT Signaling Pathway and its subsequent mutation can result in sustained activation and, therefore, unregulated cell proliferation which has been well described in colorectal cancers. Loss of function in APC, AXIN1, AXIN2, GSK3β, and RNF43 can each act to dysregulate WNT signaling, contributing to cancer development. In this study, we aimed to conduct a comprehensive, molecular evaluation of the WNT signaling pathway in colorectal cancer within age-specific cohorts with onset of CRC at 50 years old or less versus greater than 50 years old. Methods: We used published individual patient-level data of 6286 patients with colorectal cancer (CRC) from the 16 CRC datasets included in the cBioPortal database. The WNT pathway alterations, including APC, AXIN1, AXIN2, GSK3β and RNF43 mutations were considered to define the WNT mutant CRC cohort. The presence of WNT alterations according to the age (50 years old or younger vs. over 50 years) were evaluated using Chi-square tests. The association between primary tumor distribution (colon vs. rectal) and age were evaluated across patients with and without WNT pathway alterations. The effect of WNT pathway alterations on the overall survival and survival after the metastatic stage was evaluated with Kaplan-Meier survival curves. A type-I error level of 5% (p < 0.05) was considered the threshold limit for statistical significance. Results: A total of 2,630 individuals were identified with relevant clinical and molecular information. When comparing WNT alteration patterns between young-onset CRC (< 50 years old) and CRC in cohort — 50 years old, there was no statistically significant difference (p-value = 0.215). Analysis of common individual mutations in APC, AXIN1, AXIN2, GSK3β and RNF43 also showed similar incidences across age groups. However, we identified WNT alterations that were significantly more common in rectal cancers compared to colon cancer, being found in 75.9% of rectal cancer cases, regardless of age group (p-value < 0.00001). Additionally, individuals identified to have WNT alterations were found to have improved survival with a median overall survival of 58.19 months versus a median of 41.72 months in those without. Conclusions: Overall, no significant differences were found in WNT alteration expression between Young-Onset CRC versus CRC in individuals of age over 50 years which is contrary to other age-related cancer groups. WNT alterations were frequently found in rectal cancers. Furthermore, these WNT alterations were associated with better outcomes. Research Sponsor: None.

Application of GPT-4 foundation model for risk prediction and stratification in colorectal cancer. First Author: Antonio Rueda-Lara, Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain

Methods: Deep Learning Language Models (LLMs) show significant potential in analyzing complex data, particularly in oncology, where they can help cancer patients to assess their effectiveness in identifying risk subgroups. The Application of GPT-4 foundation model for risk prediction and stratification in colorectal cancer {param}, guess whether the patient is in low risk or high risk for relapse,” and the model provided dichotomic responses with the following accuracies: 2203 (36.1%) received single palliation-directed treatments, 1102 (17.9%) received a combination of palliation-directed treatments with pain management and 6308 received a combination of palliation-directed treatments with pain management and 1102 received a combination of palliation-directed treatments with pain management. Of the 21,516 patients who received single palliation-directed treatments, 50.6% and 49.4% were male and female, respectively. The mean age was 67 years. Most patients had no existing comorbidities (68.7%), lived in metropolitan areas (81.6%), had grade 2 (59.4%) and AJCC Clinical stage 4 colon cancer (32.6%). Overall, most patients received chemotherapy (50.7%) as a palliative treatment, followed by chemotherapy, radiation, pain management, or a combination of these. The extent to which these palliation-directed therapies are utilized in colon cancer remains under-explored. This study’s purpose was to understand the trends in utilization and factors associated with palliation-directed treatment modalities among patients with colorectal cancer. Methods: From the National Cancer Database, we identified patients with colon cancer who received first-line palliation-directed therapies from 2004 to 2016 without an intent to give definitive therapy. We evaluated the use of these treatments over time and compared frequencies of categorical variables using Chi square tests. A multivariate logistic regression model was also used to evaluate patient characteristics associated with the use of these treatments. Results: We identified a total of 21,516 patients receiving palliation-directed therapy among patients with colon cancer — 19,506 received single palliation-directed therapy, 908 received a combination of palliation-directed treatments without pain management and 1102 received a combination of palliation-directed treatments with pain management. Of the 21,516 patients who received single palliation-directed treatments, 50.6% and 49.4% were male and female, respectively. The mean age was 67 years. Most patients had no existing comorbidities (68.7%), lived in metropolitan areas (81.6%), had grade 2 (59.4%) and AJCC Clinical stage 4 colon cancer (32.6%). Overall, most patients received chemotherapy (50.7%) as a palliative treatment, followed by chemotherapy, radiation, pain management (14.4%) and radiation (9.7%). The utilization of chemotherapy (39.6% in 2004 to 63.1% in 2016) and pain management (9.7% in 2004 to 12.7% in 2016) increased over time while the utilization of surgery (37.1% in 2004 to 16.9% in 2016), and radiation (13.6% in 2004 to 7.3% in 2016) decreased over time. The type of facility, readmission rates, and proportion of individuals who were whites, (age ≥ 50), resided in metropolitan areas and had insurance were significantly different between groups. Male patients, patients without existing comorbidities, and patients with grade 2 tumors had higher odds of receiving surgery, radiation, or chemotherapy as palliative therapy compared to pain management. Conclusions: Utilization of first-line palliation-directed chemotherapy has increased significantly from 2004 to 2016 whereas surgery and radiation therapy use has decreased in that period. Notably, patient characteristics such as gender, absence of existing comorbidities and grade 2 tumors influence the choice of therapy. Research Sponsor: None.
Background: MSI-H tumors have a different disease biology and clinical outcomes compared to MSS/MSI-low tumors. The frequency and pattern for MSI testing and reporting is unknown. The aim of this study was to characterize the trends of MSI testing and reporting among GI cancers. Methods: From the National Cancer Database, we identified all GI cancer patients from 2010 to 2016 to determine the number of patients where MSI/MSI low or MSI-high data were available. We describe the basic tumor and disease characteristics and treatment utilization for the two groups. Results: Between 2010-2016, MSI testing was done in 140,602 patients in colon, small intestine and rectal cancers among all GI cancers. MSI testing increased significantly during this study period (11,400 in 2010; 15,021 in 2011; 17,968 in 2012; 20,810 in 2013; 21,973 in 2014; 25,012 in 2015; 28,416 in 2016). We identified a total of 120,349 patients with MSI status reported, among these three tumor types, most commonly among colon followed by rectal and then small intestinal cancers. Overall 111,694 (92.8%) were MSI/MSI-low and 8,655 were MSI-H (7.2%). Among patients with reported MSI status, 52.1% were males and 47.9% were females. The mean age was 64.4 years. Most patients were whites (87.6%) and had insurance (96.8%), no existing comorbidities (70.4%), and grade 2 (70.8%) and AJCC Clinical Stage 4 (26.1%) GI cancer. A higher proportion of GI cancer patients with MSS/MSI-low utilized chemotherapy as first course compared to those with MSI high (48.2% vs 34.0%) whereas a lower proportion of GI cancer patients with MSS/MSI-low underwent a surgical procedure compared to those with MSI high (94.7% vs 97.1%). MSI status was reported most frequently in comprehensive community cancer program (40.3%) and academic center (34.8%), followed by integrated network (16.8%) and Community Cancer program (8.1%). Conclusions: The utilization of MSI testing has increased significantly between 2010 and 2016. Among all GI cancer patients, MSI status was most frequently reported in colon, rectum and small intestinal cancers. Comprehensive community cancer centers and academic centers reported MSI status more frequently than integrated Network Cancer program and Community Cancer program. Research Sponsor: None.
A randomized controlled trial of CAPEOX vs observation in patients with early-stage colorectal cancer with positive MRD after curative surgery (Confidence III). First Author: Ke-Feng Ding, Department of Colorectal Surgery, Zhongshan Cancer Hospital. **Background:** Most patients (pts) with early-stage colorectal cancer (CRC) have a good prognosis, but some still relapse shortly after surgery. Effective methods to assess the risk of recurrence in these pts and guide adjuvant chemotherapy (ACT) decision-making are lacking. Increasing studies have shown that circulating tumor DNA (ctDNA) can detect minimal residual disease (MRD) and identify pts with a higher risk of recurrence. ACT could improve survival of MRD-positive pts with stage II CRC suggested by recent studies, whether it is appropriate for those with stage I or clinically low-risk stage II CRC remains unknown. **Methods:** CAOREME is a multicenter randomized controlled clinical trial aimed at investigating the benefit of chemotherapy for MRD-positive pts with early-stage CRC. Pts were randomly assigned to CRC-Neoadjuvant chemotherapy (ACT) or observation. All pts who did not receive neoadjuvant therapy and are deemed suitable for surveillance (i.e., ACT is not needed) will undergo a postoperative ctDNA test using Minerva MRD assay (a tumor-informed assay covering 769 cancer-related genes). Pts with mismatch repair-deficient tumors will be excluded and stage II pts should have no traditional high-risk features according to clinical practice guidelines. Pts with positive ctDNA (N = 38) will be equally randomized into two groups: treatment group (Arm A) or surveillance group (Arm B). Arm A will receive 8 cycles of CAPEOX therapy while pts in Arm B will not receive any ACT; both groups will undergo ctDNA tests at 6 months after randomization and be followed up every 3 months. The primary endpoint is 18-month recurrence-free survival, and a key secondary endpoint is ctDNA clearance at 6 months after randomization. Tumor samples from the pts will be collected for MRD assay and exploratory research. Accrual started in February 2023. Support: Genecast Biotechnology Company.

Clinical trial information: NCT05699746. Research Sponsor: None.

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A randomized controlled trial of revumenib in patients with advanced colorectal cancer and other solid tumors. First Author: Aparna Raj Parikh, Massachusetts General Hospital Cancer Center, Boston, MA

**Background:** Aberrant transcription in cancer can be reversed by targeting critical epigenetic regulators. For example, in acute leukemias driven by increased HDX gene expression, inhibition of the mei-1/2KMT2A interaction by revumenib induced differentiation in patients with heavily pretreated disease (Issa et al 2023). In solid tumors promoted by the aberrant activation of the Wnt/β-catenin pathway, in vitro data and in vivo studies have shown that small molecule inhibition of the menin-KMT2A interaction restricts growth, with potential therapeutic benefit in colorectal cancer (CRC), castration-resistant prostate cancer, estrogen receptor–positive breast cancer, gastrointestinal stromal tumors, and Ewing sarcoma. To test the therapeutic strategy of inhibiting the menin-KMT2A interaction in solid tumor malignancies, this study (NCT05731947) will evaluate revumenib in patients with CRC and other solid tumors. Revumenib is an oral, potent, selective inhibitor of the menin-KMT2A interaction. Methods: This phase 1 study is evaluating revumenib in adults aged ≥18 years with locally recurrent or metastatic CRC who have failed ≥1 prior line of therapy and in patients with other solid tumors who have failed available standard therapies. Inclusion criteria include diagnosis of microsatellite stable/proficient mismatch repair CRC or other solid tumors. Patients with CRC must be unable to receive or have disease that progressed on oxaliplatin, irinotecan, and bevacizumab; if left-sided RAS wild-type CRC, the patient must have received anti–epidermal growth factor receptor therapy. The primary phase 1 objectives are to determine the safety, tolerability, maximum tolerated dose, and recommended phase 2 dose of revumenib in patients with CRC and other solid tumors and to assess its antitumor effects. The phase 2 primary objective is to assess the antitumor effects of revumenib by blinded radiographic review. Phase 1 consists of all-comers' dose escalation (phase 1a), and signal-seeking expansion in CRC (phase 1b). Using a rolling 6 design, the revumenib starting dose will be 163 mg 3 times daily in 28-day cycles. Up to 6 patients will be enrolled in a dose cohort. Dose escalation cohorts may be expanded and used for signal seeking in non-CRC tumor types. Phase 1b in CRC will begin when a potential phase 2 dose has been identified. The disease control rate at 6 cycles and overall response rate will be used to assess antitumor activity and will determine initiation of phase 2. In phase 2, patients with advanced CRC will be randomized 2:1 to revumenib or investigator’s choice of 1 of 2 standard-of-care therapies. Patients will be followed for progression-free survival, with response assessments evaluated locally and confirmed by blinded radiographic review. As of September 5, 2023, 13 patients were enrolled in phase 1a of this study. Clinical trial information: NCT05731947. Research Sponsor: Syndax Pharmaceuticals.

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An open-label clinical trial of RP2 and RP3 oncolytic immunotherapy in combination with atezolizumab plus bevacizumab for the treatment of patients with advanced colorectal carcinoma. First Author: Heinz-Josef Lenz, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

**Background:** Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related mortality worldwide. PD-1/PD-L1 inhibition, in combination with other modalities, has demonstrated significant benefit in patients (pts) with microsatellite instability-high or mismatch repair–deficient CRC. However, these agents have limited, if any, clinical benefit in pts with microsatellite stable (MSS) or mismatch repair proficient (pMMR) CRC. RP2 is an oncolytic herpes simplex virus type 1 which expresses the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R−), granulocyte-macrophage colony-stimulating factor (GM-CSF), and an anti–CTLA-4 antibody-like molecule; RP3 additionally expresses 4-1BB and CD40 activating ligands but does not express GM-CSF. Both agents have demonstrated preliminary safety and antitumor activity in pts with solid tumors. This study will evaluate the safety and activity of RP2 and RP3 in combination with atezolizumab (Atezo) plus bevacizumab (Bev) in pts with advanced MSS/pMMR CRC (NCT05733611).

**Methods:** Pts with a histologic diagnosis of unresectable and/or metastatic CRC, with documented MSS or pMMR status, and previously treated with up to 3 standard-of-care systemic regimens will be enrolled in the RP2 + Atezo + Bev or RP3 + Atezo + Bev treatment groups (30 pts per group). Further key inclusion criteria include Eastern Cooperative Oncology Group performance status 0 to 1 and adequate hepatic, renal, and hematologic function. RP2/RP3 will be injected into tumors by direct or image-guided injection. Pts will receive 8 total doses of up to 10 ml of RP2/RP3, with a first dose concentration of 1 × 10^7 plaque-forming units (PFU)/ml, followed by 3 doses of 1 × 10^7 PFU/ml every 2 weeks, and then 4 doses of 1 × 10^7 PFU/ml every 3 weeks. Pts may receive a second course of up to 8 injections of RP2/RP3 if study criteria are met. Bev will be administered starting on week 1; Atezo will be administered starting week 7. The primary endpoint is objective response rate; secondary endpoints are safety, overall survival, progression-free survival, duration of response, and complete response rate. Antitumor activity will be evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 as modified for this study. Safety will be assessed by physical examination, clinical laboratory evaluations, vital signs, and monitoring for adverse events (AEs); including serious AEs. Clinical trial information: NCT05733611. Research Sponsor: Replimune, Inc.
Zanzalitinib (XL092) plus atezolizumab versus regorafenib in previously treated MSS/MSI-low metastatic colorectal cancer (mCRC): The randomized phase 3 STELLAR-303 study. First Author: Anwar Aseed, University of Pittsburgh Medical Center, Pittsburgh, PA

**Background:** Patients with microsatellite stable/microsatellite instability-low (MSS/MSI-low) mCRC account for ~95% of mCRC cases, and there is a significant unmet need in patients with treatment-refractory MSS/MSI-low mCRC. Although immune checkpoint inhibitors (ICIs) have shown limited activity in this patient population, the addition of tyrosine kinase inhibitors (TKIs) may increase sensitivity to ICIs by promoting an immune-permissive tumor microenvironment. Furthermore, TKI-ICI combinations have demonstrated encouraging clinical activity in patients with mCRC, particularly in subgroups of patients without liver metastases (LM). Most recently, in the phase 3 LEAP-017 study of patients with non-MSI-high/mismatch repair defect (dMMR) mCRC, although pembrolizumab + lenvatinib did not improve overall survival (OS) vs standard of care, subgroup analysis suggested the potential for clinical benefit in patients without LM (Kawazoe et al, ESMO-WCIG 2023). Zanzalitinib is a novel multi-kinase inhibitor targeting VEGFR, MET, and the TAM kinases (TYRO3, AXL, MER). In a phase 1 study, zanzalitinib alone in and combination with atezolizumab (an anti-PD-L1 ICI) showed promising preliminary anti-tumor activity and a manageable safety profile across multiple tumor types (Sharma et al, ESMO 2022). **Methods:** STELLAR-303 (NCT05425940) is a global, randomized, open-label phase 3 study to assess the efficacy and safety of zanzalitinib + atezolizumab versus regorafenib in adult patients with MSS/MSI-low mCRC. Patients must have documented MSI/MMR status (non-MSI-high/dMMR) and RAS status by tissue-based analysis, measurable disease per RECIST v1.1, ECOG PS 0 or 1, and radiographic progression during/after or intolerance to standard of care treatments for mCRC. Prior regorafenib, trifluridine/tipiracil, or PD-L1/PD-1 ICI are not allowed. Patients with or without active LM at baseline are eligible; those with definitively treated LM (includes surgical resection, microwave/radiofrequency ablation, or stereotactic body radiation therapy, but not intratumoral or chemotherapy alone or continued) have at least 1.5 cm active LM if treated 6 months before enrollment with no evidence of radiologic progression on subsequent imaging. Patients are randomized 1:1 to receive zanzalitinib + atezolizumab or regorafenib. Planned enrollment is 874 patients; number of patients with LM will be capped to ensure results are relevant to the real-world efficacy and safety of zanzalitinib + atezolizumab in patients with LM. The key secondary efficacy endpoint is OS in all randomized patients. A hierarchical testing strategy will be employed for primary and key secondary endpoints. Safety will also be assessed. Enrollment is ongoing in the US, Europe, and Asia-Pacific region. Clinical trial information: NCT05425940. Research Sponsor: Exelixis, Inc.

Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study: A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability-high (MSI-high/mismatch repair deficient (dMMR) mCRC, 6 months before enrollment with no evidence of radiologic progression on follow up have been reduced; as has measurable disease per RECIST. The primary endpoint is PFS. Assuming the atezo monotherapy control arm has a 48% PFS at 24 mos as assessed by site investigator, we have 80% power to detect a hazard ratio of 0.6 (equivalent to 64.4% PFS at 24 mos) with alpha 0.025 one-sided. Stratification factors include BRAF/VEGF status, metastatic site, and prior adjuvant CRC therapy. Secondary endpoints include objective response and duration of response. AEs will be evaluated it as monotherapy and combination therapy in patients (pts) with advanced solid tumors. The Frost trial is expected to elucidate the safety and oncologic efficacy of mFOLFIRINOX compared to mFOLFOX 6 as adjuvant treatment for high-risk stage III colon cancers, and provide evidence about this treatment, and contribute to improve the progresses ultimately. **Clinical trial information:** NCT05179889. Research Sponsor: The Korean Society of Coloproctology, Korea National Enterprise for Clinical Trial UG1CA189867, U24CA196067; Genentech, Inc. Clinical trial information: NCT01992729. Research Sponsor: NIH; Genentech, Inc.

mFOLFIRINOX versus mFOLFOX 6 as adjuvant treatment for high-risk stage III colon cancer (FROST trial): Study protocol for an open label, multicenter, randomized, phase II study. First Author: Kyung-ha Lee, Department of Surgery, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejon, South Korea

**Background:** Patients with high-risk stage III colon cancer have a significantly poorer prognosis than those with stage II or low-risk stage III colon cancer. Despite this distinction, most guidelines recommend similar adjuvant treatment approaches for all stages, and there is a dearth of research focusing on high-risk stage III colon cancer and the potential for improved prognosis through more intensive adjuvant treatment. Given the proven efficacy of triplet chemotherapy in metastatic colorectal cancer, this study aims to assess the effectiveness and toxicity of modified 5-fluoropyrimidine (5-FU)/leucovorin plus irinotecan and oxaliplatin (mFOLFIRINOX) in comparison with the current standard of care—modified oxaliplatin and 5-FU (mFOLFOX-6)—as an adjuvant treatment for patients diagnosed with high-risk stage III colon cancer. This multicenter, randomized (1:1), open-label, phase II trial aims to compare the adjuvant treatment efficacy of mFOLFIRINOX and mFOLFOX-6 in patients with high-risk stage III colon cancer. The trial aimed to enroll 312 eligible patients aged between 20 and 70 years with an Eastern Cooperative Oncology Group performance status of 0-2, or between 70 and 75 years with an Eastern Cooperative Oncology Group performance status of 0. All patients underwent radical resection and were randomized into two arms: Arm A experimental arm, received 12 cycles of mFOLFIRINOX every 2 weeks, while arm B, the reference arm, received 12 cycles of mFOLFOX 6 every 2 weeks. The primary endpoint of this study was the 3-year disease-free survival, whereas the secondary endpoints included assessing the 3-year overall survival and treatment toxicity. Discussion: The Frost trial is expected to elucidate the safety and oncologic efficacy of mFOLFIRINOX compared to mFOLFOX 6 as adjuvant treatment for high-risk stage III colon cancers, and provide evidence about this treatment, and contribute to improve the progresses ultimately. Clinical trial information: NCT05067283. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD).
Node-sparing modified short-course radiotherapy combined with CAPOX and tislelizumab for locally advanced MSS of middle and low rectal cancer (mCRC). Methods: A single-center, open-label, randomized, phase II study of node-sparing modified short-course radiotherapy combined with CAPOX and tislelizumab was designed. The primary endpoint was assessment of safety and tolerability (primary). Secondary endpoints were T-cell and tumour regression grade, organ preservation rate, and disease-free survival (DFS) at 12 months. A total of 24 participants were enrolled. Patients were randomized 2:1 into 2 arms, respectively; experimental treatment (E + C + N) or standard treatment (E + C). The primary endpoint DFS will be assessed at 12 months and compared between the two arms using the log-rank test. Conclusion: This trial is designed to evaluate the safety and efficacy of adding total ablative therapy (TAT) of all sites of disease in patients with oligometastatic colorectal cancer with local therapy, which is provider biased and not evidence based, and in patients with limited metastatic CRC that is deemed inoperable or those with additional disease outside of the liver or lungs, the role of local ablative therapies, including microwave (MWA) and stereotactic body radiation therapy (SBRT), to render patients disease free is less clear. Future, despite the long history of treating oligometastatic CRC with local therapy, which is provider biased and not evidence based, questions remain regarding the benefit of extending the paradigm of metastatic directed therapy to patients with more extensive disease. This trial seeks to use a pragmatic randomized phase II design approach that mirrors the current clinical dilemma. This study is designed to evaluate the safety and efficacy of adding total ablative therapy (TAT) of all sites of disease to standard of care systemic treatment in those with limited metastatic CRC.

TPS234
Trials in Progress Poster Session
SWOG S2107: Randomized phase II trial of encorafenib and cetuximab with or without nivolumab for patients with previously treated, metastatic colorectal cancer Methods: This is a multinational, multicenter, phase II trial. A total of 240 patients with mCRC with progression on or after one line of systemic therapy will be randomized 2:1:1 to receive either: Arm 1: encorafenib 460 mg PO daily for 30 days, followed by 240 mg PO daily dosing, plus cetuximab 400 mg/m² IV on day 1 of every 4 weeks; Arm 2: encorafenib 460 mg PO daily for 30 days, followed by 240 mg PO daily dosing, plus cetuximab 400 mg/m² IV on day 1 of every 4 weeks, and nivolumab 240 mg IV on day 1 of every 4 weeks; Arm 3: standard of care systemic therapy alone. The primary endpoint is ORR as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The pre-planned secondary endpoints include: PFS and OS as assessed by RECIST v1.1, duration of response, and safety as assessed using NCI-CTCAE v5.0. The trial is powered to detect a 10% improvement in ORR in Arm 2 compared to Arm 1, with a 1-sided alpha of 0.026. The trial is expected to accrue 155 patients in each of the 3 arms. The expected median follow-up is 12 months. Enrollment began in October 2021. Conclusion: SWOG S2107 (NCT05132423) is a phase II trial of encorafenib and cetuximab with or without nivolumab for patients with previously treated, metastatic colorectal cancer. This phase II trial will provide evidence on the feasibility of adding nivolumab to the combination of encorafenib and cetuximab in patients with mCRC with disease progression after standard of care treatment. This will help inform the design of subsequent phase III trials.
Combining low-dose regorafenib with pembrolizumab for patients with MSI-H colorectal cancer: REGPEM-CRC-01. First Author: Ibrahim Halim Sahin, University of Pennsylvania Medical Center, Philadelphia, PA

Background: Treatment for microsatellite instability-high (MSI-H)/ mismatch repair deficient (MMR-D) colorectal cancer (CRC) has rapidly evolved in the last decade. The KEYNOTE 177 trial recently established pembrolizumab as a frontline therapy for patients with MSI-H CRC. However, in this study, approximately 40% of patients were noted to have disease progression within 6 months of treatment. Furthermore, an additional 10% of patients received subsequent recurrent therapy. The objective was to determine the most effective regimen to improve outcomes for patients with MSI-H CRC. Preclinical studies have shown vascular endothelial growth factor (VEGF) signaling to be overtactive in MSI-H compared to MSS CRC (Hansen et al. Colorectal Dis. 2011). Moreover, exploratory analysis of CALGB-80405 and PARADIGM trials showed that patients with MSI-H CRC were more likely to benefit from anti-VEGF therapy than those with MSS disease. Regorafenib, an FDA-approved agent for patients with mCRC, is a potent VEGF inhibitor with immunomodulatory effects on the tumor microenvironment. We hypothesized that adding low-dose regorafenib to pembrolizumab as frontline therapy may create synergistic activity in addition to the known clinical activity of each agent in MSI-H CRC. Methods: In the lead-in arm of this prospective study, 22 patients will be enrolled. Patients will receive regorafenib 60 mg daily on days 1–14 (2 weeks on) followed by 7 days off (1 week off) in combination with pembrolizumab 200 mg in the cycle 1. In the following cycles, patients will receive regorafenib 90 mg daily for 2 weeks on in combination with pembrolizumab 200 mg every 3 weeks. The primary outcome for the lead-in arm is overall response rate for 6 months of treatment by RECIST 1.1. The alternative hypothesis test will be conducted for futility, assuming that we will reject the null hypothesis of a target ORR only if we have strong evidence. In this study, we assume a null hypothesis that ORR is 0.60, which would reflect significant clinical improvement over the current benchmark of 0.55. The alternative hypothesis is ORR is greater than 0.60. For the lead-in phase of the study, the emphasis is on controlling Type I error to be small, approximately 0.05. In the randomized phase of the study, patients will receive pembrolizumab monotherapy or pembrolizumab in combination with regorafenib 90 mg. The sample size for the randomized phase of trial was determined based on an assumed median of PFS of 28 months with pembrolizumab and pembrolizumab combination (investigational arm). The standard of care pembrolizumab monotherapy results in a median PFS of 16 months when given as a first-line therapy. We hypothesize the proposed treatment will increase median PFS to 28 months from 16 months (N=132; H0: 16 months vs., H1: 28 months; Type I error: 0.05, power 80%). Clinical trial information: NCT06006923. Research Sponsor: None.
TPS241  Trials in Progress Poster Session

NSABP C-14/Exact Sciences 16-002: CORRECT-MRD II—Second colorectal cancer clinical validation study to predict recurrence using a circulating tumor DNA assay to detect minimal residual disease. First Author: Mohamed E. Salem, Levine Cancer Institute, Charlotte, NC

Background: Detectable circulating tumor DNA (ctDNA) after resection of early-stage solid tumors has been associated with very high risk of recurrence, suggesting ctDNA is evidence of minimal residual disease (MRD). Several studies are ongoing to investigate the role of ctDNA in the optimal management of patients (pts) with colorectal cancer using different assay technologies. Methods: This is a prospective, observational, multicenter study in the United States and Canada of 750 pts who have undergone complete surgical resection for stage II or III colorectal cancer, who have FFPE tissue available from the primary resection sufficient for a novel bespoke MRD assay and are willing to provide serial whole blood specimens for ctDNA analysis. Participants are asked to provide study specimens after definitive surgical resection, pre-recurrence follow-up, and clinical recurrence (if applicable). Recently amended eligibility criteria include inclusion of rectal cancer pts who have completed neo-adjuvant therapy and surgical resection, as well as enrollment of all stage II and III pts regardless of microsatellite stability status. The Oncotype Colon Recurrence Score® will be assessed on all pts from their surgical specimen, if criteria are met for this testing. ctDNA will be analyzed with an NGS-based tumor-informed MRD assay that identifies somatic genomic alterations from DNA derived from the patient’s tumor tissue, subtracts germline variants, and detects a selected subset of tumor-specific (bespoke) ctDNA in their blood. All primary tumor specimens will undergo full exome and transcriptome sequencing using the Onco ExTra assay. If there is evidence of disease recurrence, the metastatic tissue will also undergo Onco ExTra testing and results will be shared with participants. The primary objective is to validate the association of post-definitive therapy and pre-recurrence follow-up ctDNA positivity with recurrence-free interval (RFI). Further objectives are to assess: the sensitivity and specificity of ctDNA positivity for subsequent clinical recurrence; contribution of post-surgery baseline, post-adjunctive therapy, and pre-recurrence follow-up ctDNA results on RFI; time from positive ctDNA to clinical recurrence in participants who had a positive ctDNA result; and to compare the Oncotype Colon Recurrence Score estimate of 3-year recurrence risk with the observed 3-year recurrence rate. The primary analysis will use a Cox proportional hazards regression applied to the RFI with ctDNA result (positive or negative) measured after surgery, or end of adjunctive therapy if received, and serially after that as a single, time-dependent covariate. Enrollment has currently surpassed the 50% target. Protocol#: NSABP C-14 / Exact Sciences 16-002 NCT#: 05210283. Support: NSABP Foundation, ExactSciences. Clinical trial information: NCT05210283. Research Sponsor: NSABP Foundation, Inc. ExactSciences.

TPS242  Trials in Progress Poster Session

MRD assay to evaluate recurrence and response via a tumor informed assessment: MARIA-Colorectal Cancer Observational trial. First Author: Edward D. Esplin, Invitae, San Francisco, CA

Background: The detection of ctDNA in patients with colorectal cancer (CRC) is emerging as a potential biomarker to identify patients at high risk of relapse, assess treatment response and monitor for recurrence. Solid tumors are currently monitored by imaging studies, tumor markers and clinical symptoms and recent studies suggest tumor-informed molecular residual disease (MRD) testing may outperform these current methods and may serve as a prognostic biomarker to aid in the identification of patients at high risk of relapse (Reinert et al, 2019; Christensen et al, 2019; Coombes et al, 2019). Recent studies have demonstrated that tumor-informed MRD testing can detect relapse prior to detection with imaging in CRC and while interventional trials are needed, this may provide an opportunity for therapeutic intervention (Reinert et al, 2019; Kotani et al, 2023). This study utilizes the Invitae Personalized MonitoringTM (PCM) test, a highly sensitive tumor-informed MRD test (Zhao et al, 2023), to monitor early stage CRC patients. Methods: MARIA is a multi-site, prospective, observational trial in the United States of 200 newly diagnosed patients with early stage (high risk stage II, stage III and stage IV oligometastases) CRC undergoing curative intent treatment. Formalin fixed paraffin embedded (FFPE) tissue from the biopsy or surgical specimen is utilized to create the PCM test. Tumor tissue and a matched normal blood sample will undergo whole exome sequencing to identify 18-50 unique tumor variants to create a patient specific panel (PSP) for ctDNA analysis. Participants are asked to provide serial plasma specimens for ctDNA analysis at baseline, post surgical landmark and surveillance time points. A clinical report will be provided to the ordering physician. Physicians will be asked to complete a case report form for each participant when the first result is reported and every 6 months. The primary endpoint is to evaluate the correlation between the PCM test result at the landmark timepoint and the patient’s 24 month recurrence risk. Secondary endpoints include evaluating the impact on patient outcomes attributable to MRD result-based changes to treatment or clinical management, correlating between the PCM result at the baseline time point and patient recurrence risk and outcomes and investigating the lead time of PCM positivity over clinical/imaging based evidence of recurrence. Active enrollment started in March, 2022. Clinical trial information: NCT05219734. Research Sponsor: Invitae.

TPS243  Trials in Progress Poster Session

NRG-GI008: Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-NORTH AMERICA). First Author: Christopher Hanyoung Lieu, University of Colorado Cancer Center, Aurora, CO

Background: Currently, there are no biomarkers validated prospectively in randomized studies for resected colon cancer (CC) to determine need for adjuvant chemotherapy (AC). Circulating tumor DNA (ctDNA) represents a highly specific and sensitive approach (especially with serial monitoring) for identifying minimal/molecular residual disease (MRD) post-surgery in CC patients (pts), and may outperform traditional clinical and pathological features in prognosticating risk for recurrence. CC pts who do not have detectable ctDNA (ctDNA-) are at a much lower risk of recurrence and may be spared the toxicities associated with AC. Furthermore, for CC pts with detectable ctDNA (ctDNA+) who are at a very high risk of recurrence, the optimal AC regimen has not been established. We hypothesize that for pts whose CC has been resected, ctDNA status may be used to risk-stratify for making decisions about AC. Methods: In this prospective phase II/III trial, up to 1,912 pts with resected stage IIB, IIC, and III CC will be enrolled. Based on the post-operative ctDNA status using personalized and tumor-informed assay (Signatera®, bespoke assay), those who are ctDNA- (Cohort A) will be randomized to immediate AC with fluoropyrimidine (FP)+oxaliplatin (Ox) for 3-6 mos per established guidelines vs. serial ctDNA monitoring. Patients who are ctDNA+ post-operatively or with serial monitoring (Cohort B) will be randomized to FP+Ox+ vs. more intensive AC with addition of irinotecan (I) for 6 mos. One cycle of chemotherapy is allowed while awaiting ctDNA testing results for cohort assignment. The primary endpoints for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) (phase III) in the immediate vs. delayed AC arms. The primary endpoint for Cohort B is DFS in the FP+Ox vs FP+Ox+I arms for both phase II and phase III portions of the trial. Secondary endpoints include prevalence of detectable ctDNA post-operatively, time-to-event outcomes (overall survival and time to recurrence) by ctDNA status, and the assess-ment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, as well as post-operative plus serial matched/normal blood samples, will be collected for exploratory correlative research. Active enrollment across the NCTN started in June 2020. CIRCS sites joining in August 2023. Support: U10-CA-180968, -180922; UG1CA-189867; Natera, Inc. Clinical trial information: NCT05174169. Research Sponsor: NIH; Natera, Inc.
Chemotherapy plus camrelizumab versus chemotherapy alone as neoadjuvant treatment for resectable esophageal squamous cell carcinoma (ESCORT-NEO): A multi-center, randomized phase III trial. First Author: Yao Li, Department of Thoracic Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the January 20, 2024, issue of the Journal of Clinical Oncology.

Pembrolizumab plus FLOT vs FLOT as neoadjuvant and adjuvant therapy in locally advanced gastric and gastroesophageal junction cancer: Interim analysis of the phase 3 KEYNOTE-585 study. First Author: Salah-Eddin Alsabban, Department of Gastrointestinal Oncology, Department of Gastrointestinal Oncology, Department of Gastrointestinal Oncology, Department of Gastrointestinal Oncology.

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the January 20, 2024, issue of the Journal of Clinical Oncology.
OS, median, HR (95% CI) 

| OS and PFS | ITT | n = 749 | ESCC | n = 448 | ESCC and OS + PFS | n = 589 | \( \geq 10 \) | n = 338 | \( \geq 10 \) | n = 296 |
|---|---|---|---|---|---|---|---|---|---|
| OS, median, HR (95% CI) | 0.72 (0.62-0.84) | 0.71 (0.60-0.85) | 0.65 (0.52-0.80) | 0.60 (0.46-0.76) |
| 5-year OS rate, a,b,c | 10.6 vs 3.0 | 11.8 vs 3.4 | 12.8 vs 3.8 | 13.8 vs 3.7 |
| PFS, median, HR (95% CI) | 0.64 (0.54-0.75) | 0.65 (0.54-0.78) | 0.51 (0.40-0.64) | 0.53 (0.41-0.69) |

**Table 1**: Progression-free survival and overall survival according to the number of cycles for patients with advanced esophageal squamous cell carcinoma treated with nivolumab plus ipilimumab compared with chemotherapy. **ITT**: intention-to-treat analysis; **ESCC**: esophageal squamous cell carcinoma; **OS**: overall survival; **PFS**: progression-free survival; **HR**: hazard ratio; **a,b,c**: Adjusted for age, sex, and ECOG PS; **CI**: confidence interval.

**Results**: Overall, 749 pts were randomized to receive pembro + chemo (n = 373) or pbo + chemo (n = 376). Median time from randomization to data cutoff was 58.8 mo (range, 49.2-70.0). One thousand seven hundred and forty-nine patients were randomized to the two arms, with a median follow-up of 3.5 years for both arms. The primary endpoint of OS was met, with a median OS of 12.8 months for the pembro + chemo arm and 9.8 months for the pbo + chemo arm (HR 0.72 [95% CI 0.62-0.84]). The 5-year OS rates were 10.6% and 3.0%, respectively. The median PFS was 9.8 months for the pembro + chemo arm and 7.8 months for the pbo + chemo arm (HR 0.69 [95% CI 0.54-0.88]). The 5-year PFS rates were 55.0% and 40.0%, respectively. Grade 3-5 treatment-related AEs occurred in 26% (17.9%) of pts in the pembro + chemo arm and 25% (16.7%) in pts with pbo + chemo. AEs led to death in 2 (2.4%) and 1 (1.4%) of pts in the pembro + chemo vs pbo + chemo arms, respectively. **Conclusions**: After 5 yrs, the use of pembro + chemo showed durable efficacy versus pbo + chemo, with no new safety concerns in pts with unresected advanced esophageal cancer. Long-term results continue to support use of pembro + chemo for advanced esophageal cancer. Clinical trial information: NCT03189719. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ, USA.
Nivolumab (NIVO) plus (+) chemotherapy (chemo) or ipilimumab (IPI) vs chemo as 1L treatment for advanced esophageal squamous cell carcinoma (ESOPHAGEAL AND GASTRIC CANCER 63s).

Prevalence of modifiable risk factors of Hispanic adult patients admitted with gastric cancer in the US. First Author: Alejandro Nieto Dominguez, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL.

Background: More than 19% of the US population is comprised of Hispanic individuals. For decades, cancer incidence has been increasing in this population, including cancers associated with infection (gastric, hepatic, cervical) and resulting from delayed screening (colorectal, cervical, breast). Risk factors associated with gastric cancer include H. pylori, obesity, alcohol, and tobacco use. However, evidence has not been consistently reported for risk factor decrease studies that have shown a decrease in the incidence of gastric cancer in Hispanics at a younger age.

Methods: We used the 2016-2019 National Inpatient Sample (NIS) database to stratify patients with gastric cancer by age, ethnicity, and comorbidities. Results: There were 77,450 (45.6%) gastric cancers among Hispanic patients, of which 45.6% (34.8%) were ages 18-44 (group 1), 28,370 (36.4%) 45-64 years old (group 2), and 25,790 (31.6%) were over 65 (group 3). Group 1 was comprised of 29.4% White, 34.3% Hispanic, 14.5% Black, and 16.1% Asian or Pacific Islander patients. Group 2 consisted of 46.7% White, 19.1% Hispanic, 17.8% Black, and 16.2% Asian or Pacific Islander patients. Group 3 comprised of 29.4% White, 34.3% Hispanic, 14.5% Black, and 21.7% Asian or Pacific Islander patients. Group 1 had the highest percentage of White patients (56.0%) and lowest percentage of Hispanic individuals (12.9%). Group 3 also consisted of 15.1% Black and 16.0% Asian or Pacific Islander patients. In Hispanics with gastric cancer, there was a predominance of H. pylori-associated antrum tumors (8.6% in group 1 vs 3.6% in 2.1% in groups 2 and 3 respectively (p = 0.06)). Incidence of smoking increased with age (19.1% in group 1, 28.1% in group 2 and 31.1% in group 1 (p = 0.00)) as did incidence of diabetes (8.1% in group 2, 26.4% in group 2 and 36.0% in group 3 (p = 0.00)). Alcohol use was 3.0% in group 1, 4.3% in group 2 and 3.5% in group 3.

Conclusions: Gastric cancer accounts for approximately 1.5% of all new cancers diagnosed in the US, with a higher incidence in older White populations. However, this study demonstrates that there is a large proportion of young Hispanics with gastric cancer who have higher associated instances of H. pylori. This suggests the need for further research to determine if there is utility in screening for H. pylori in asymptomatic young gastric cancer patients to decrease the burden of gastric cancer in this population. Research Sponsor: None.

Disparities in survival in Asian American, Native Hawaiian, and Pacific Islander patients with gastric adenocarcinoma. An NCDB analysis. First Author: Anjali Mishra, Creighton University School of Medicine, Omaha, NE.

Background: Asian American, Native Hawaiian, and Pacific Islander (AANHPI) individuals exhibit stark disparities in gastric cancer mortality rates, with AANHPI men facing a two-fold higher risk of death and AANHPI women encountering a 2.5-fold elevated risk compared to their Non-Hispanic White (NHW) counterparts. However, the AANHPI community is a diverse group, including over 21 ethnic groups. Here, we identify disparities among AANHPI subpopulations with gastric adenocarcinoma.

Methods: The National Cancer Database, which gathers data from over 1,500 accredited hospitals and facilities across the United States, this retrospective cohort study identified 141,906 patients with gastric adenocarcinoma (ICD code ‘8140’). Races listed as ‘unknown/other’ or ‘Other Asian’ were excluded. Kaplan Meier and Cox Regression analyses were performed. Results: This study computed mean overall survival (OS) of NHW (n=111,337), East Asian (EA) (n=3,745), South Asian (SA) (n=760), Southeast Asian (SEA) (n=1,379), and Native Hawaiian or Pacific Islander (NPHI) (n=325) patients with gastric adenocarcinoma. When aggregated, AANHPI had statistically significant improved OS compared to NHW (21.6 months vs 14.1 months, p<0.001). After disaggregating, the mean OS was 26.9 months for EA; 21.3 months for SA; 14.5 months for SEA; and 14.3 months for NPHI. Only SA and EA had significantly improved OS than NHW (p<0.001 for both). SEA and NPHI had significantly worse outcomes than NHW (<0.001 for both) and SA (p=0.03 for SEA, and p = 0.03 for NPHI). Multivariate analysis accounted for age at diagnosis, insurance status, median income quartile, Charlson-Deyo comorbidity score, facility type, stage at diagnosis, and time to treatment. SA (HR=0.92, 95% CI 0.726 to 0.925, p = 0.001), EA (HR=0.64, 95% CI, 0.609 to 0.68; p <0.001), and SEA (HR=0.896, 95% CI 0.821 to 0.978, p=0.014) had lower survival hazard ratios compared to NHW. NPHI (HR=0.931, 95% CI 0.775 to 1.119, p=0.448) did not have a statistically significant relationship compared to NHW. EA (HR = 0.896, 95% CI 0.548 to 1.474, p=0.603) and SEA (HR = 0.801, 95% CI 0.557 to 1.179, p=0.007) had significantly lower survival hazard ratios compared to NHPI. Conclusions: Survival disparities exist among AANHPI subgroups with gastric adenocarcinoma. At first glance, OS appeared significantly greater for AANHPI patients compared to NHW. However, disaggregation of AANHPI subpopulations revealed that SEA and NPHI had survival differences compared to NHW. Further analysis for socioeconomic factors, NPHI had significantly worse hazard ratios compared to South Asian and East Asian. This highlights the need to disaggregate AANHPI data so that disparities among these diverse subpopulations can be identified, investigated and ultimately addressed. Research Sponsor: None.

Inpatient outcomes of metastatic epidermal spinal cord compression in patients with gastric cancer compared to patients with other solid cancers. First Author: Ayobami Gbenga Olafimihan, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL.

Background: Metastatic epidermal spinal cord compression (MESCC) is an oncologic emergency which can be associated with poor outcomes for cancer patients. Our aim was to study the differences in outcomes of MESCC in patients with gastric cancer (GC-MESCC) compared to those with other solid malignancies. Methods: Healthcare Cost and Utilization Project-Nationwide Inpatient Sample database (2016-2020) was used to identify all solid (breast, prostate, lung, gastrointestinal, renal and thyroid) cancer patients who presented with spinal cord compression. Multivariate logistic regression was used to evaluate differences in socio-demographics, medical comorbidities and outcomes between MESCC in gastric cancer patients and those with other solid cancers. The primary outcome included inpatient mortality, length of stay (LOS), and total hospital charges. Results: 78,385 patients with the above solid cancers were admitted for cancer-related spinal cord compression. Among them, 710 had gastric cancer. Patients with gastric cancer were younger (Mean age: 59.1 vs 66.3 years, p < 0.001). They had higher prevalence of anemia (56 vs 41%, p = 0.001), protein energy malnutrition (28.9 vs 18.9%, p < 0.001), and higher rates of blood transfusion (16.2 vs 9%, p = 0.003). On multivariate regression, those with GC-MESCC had two-fold higher odds of all-cause mortality (adjusted odds ratio (aOR): 2.0; 95% CI: 1.0-3.96, p = 0.034). On subgroup analysis, mortality was about four times higher for females with GC-MECC relative to the other group (aOR = 3.8, 95% CI: 1.69-8.52, p = 0.001). There was a trend towards increased LOS (8.9 vs 7.8 days) and THC ($115,805 vs $96,074) but it was not statistically significant. Compared with the other cohort, GC-MECC patients had higher rates of blood transfusion (16.2% vs 9%, p = 0.003). Conclusions: Metastatic epidural spinal cord compression is associated with increased odds of inpatient mortality in gastric cancer patients compared to those with other solid malignancies. Hence, these patients ought to have urgent intervention and close monitoring to prevent adverse outcomes. Research Sponsor: None.

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Background: Despite the growing awareness in health disparities, racial and ethnic disparities in the treatment, insurance status, income, residence area, and Charlson/Deyo score. Pearson (NH) patients in the National Cancer Database with esophageal cancer between 2010-2017. Over this period, we observed a decrease in gastric cancer-related hospitalizations from 42,865 to 39,885. However, among Hispanics, there was a significant increase in hospitalizations from 6,309 to 6,930 cases (annual percentage change [APC] of 1.8%, P < 0.001). Notably, there was a significantly higher in hospital mortality odds for African-American (AA) (aOR 1.15, 95% CI: 1.03-1.29), Asian (aOR 1.23, 95% CI: 1.06-1.42), and all other races (aOR 1.35, 95% CI: 1.13-1.60). Surgical interventions differed among racial groups, with AA having lower odds of undergoing partial gastrectomy (aOR 0.71, 95% CI: 0.65-0.80), and Asians having higher odds of receiving partial gastrectomy (aOR 1.59, 95% CI: 1.38-1.80). Also, differences existed between AA and Hispanics. AA had the highest cure 92% vs. 79% at 0.01 days, followed by Native American/Other (NA) at 7.5±0.2 days. The financial impact of also differs, with Asians incurring the highest mean total charges at 101,436.8±2,353.8, followed by NA at 93,107.2±3,954.7. The total hospital charge burden of gastric cancer increased from 3,662.8 million to 3,890.0 million (APC 1.04%). The white population experienced the highest increase in this burden, from 879,900 million to 1,990.0 million (APC of 1.10%). Conclusions: Despite an overall decrease in gastric cancer hospitalizations, our study reveals notable disparities across racial and ethnic groups. Hospitalizations increased among Hispanics, and NA, Asians, and NA faced higher mortality odds. AA experienced the longest lengths of stay, while Asians bore the highest mean total charges. These findings highlight the need for targeted interventions to mitigate these disparities. Research Sponsor: None.

257 Poster Session

Unveiling survival strategies: The impact of treatment modalities on patients with esophageal cancer and the role of racial disparities. First Author: Yen-Chen Chiu, National Taiwan University Hospital, Taiwan, ROC

Background: Managing esophageal cancer (EC) involves neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy as the standard of care. However, some patients may remain unsuitable for esophagectomy. This study explores real-world outcomes in EC patients across different treatments, providing prognostic factors and showing potential racial disparities. Methods: A total of 502 patients diagnosed with locally advanced EC between 2004-2017 were extracted from the National Cancer Database. The cohort was stratified into three groups: nCRT followed by esophagectomy, definitive RT (dCRT), single-modality RT. The dataset included 24,318 patients who received nCRT with esophagectomy or dCRT (N=17,554) and 1,971 patients who received single-modality RT. Endpoints included overall survival (OS). Cox Proportional Hazards Model was employed for multivariate survival analysis. Chi-square test was applied to the covariate demographic data. Results: nCRT followed by esophagectomy significantly improved OS compared to dCRT (hazard ratio [HR] 0.87, 95% CI: 0.78-0.97, p < 0.001). Single-modality RT had an HR of 1.10 (95% CI: 1.06-1.15, p < 0.001). Conclusions: Real-world data analysis underscores the effectiveness of nCRT followed by esophagectomy in providing the best survival benefit for EC patients compared to dCRT or RT alone. Racial disparities emerged as significant factors influencing cancer survival outcomes. These identified factors including race and age can assist clinicians in making better-informed decisions regarding treatment pathways for specific patient populations. Research Sponsor: None.

Variable n= Hazard Ratio p-value

Age 50-65 1,495 1.02 (1.01, 1.03) < 0.001
Race White 1,500 1.10 (1.06, 1.15) < 0.001
Asian 1,174 1.18 (1.12, 1.24) < 0.001
Black 1,193 1.27 (1.20, 1.34) < 0.001
Hispanic 906 1.32 (1.24, 1.40) < 0.001

258 Poster Session

Esophageal cancer in Hispanics: A propensity score matched analysis of the National Cancer Database. First Author: Kenneth Lee Meredith, Jefferson Cancer Institute, Florida State University College of Medicine, Sarasota, FL

Background: Hispanics are the fastest-growing minority and largest ethnic group accounting for 19.1% of the US population. The American Cancer Society estimated 21,560 new cases of esophageal cancer (EC) in the US in 2023. Hispanics reported to be at high risks for EC. We sought to interrogate the demographic patterns of esophageal cancer in Hispanics. Additionally, we sought to examine evidence of socioeconomic disparities and differential therapy. Methods: We identified Hispanic vs Non-Hispanic (NH) patients in the National Cancer Database with esophageal cancer between 2005-2018. Variables compared were age, sex, tumor data, surgical intervention, type of treatment, insurance status, income, residence area, and Charlson/Deyo score. Pearson’s Chi-square test was used to compare categorical variables. Groups were statically equated with propensity score-matched analysis (PSM). Survival analysis was estimated by Kaplan-Meier method and associated log-rank test. Significance was considered at p-value < 0.05. Results: We identified 66,335 patients with a median age of 63 years (19-90). Hispanics represented 4.2% (2,786) of the entire patient cohort. In this US population we identified significant disparities between Hispanic and NH groups. Differences among Hispanics included higher prevalence of squamous EC (22% vs 19% p < 0.001), higher likelihood of stage IV disease (40.7% vs. 34.8% p < 0.001), younger age p < 0.001, higher uninsured status (10.3% vs 3.3%) with income < $40,227 (27.5% vs 16.9%) p < 0.001 when compared to NH. However, Hispanics were less likely to have surgical intervention (20.5% vs 27.5%) p < 0.001, receive neoadjuvant therapy (61.8% vs 72%) and overall, less likely to receive any type of treatment (30.1% vs 26.1%) when compared to NH p < 0.001. Time to treatment was delayed in those Hispanics who were uninsured 37 weeks (22.5) compared to those with private insurance 31 weeks (20.4) p < 0.001. Multivariate analysis revealed that any treatment, insurance status, and lower income were all predictors of survival. Treated Hispanics demonstrated no difference in survival then their treated non-Hispanic counterparts (median survival 18.5 vs 18.7 months) with overall 5 year survival at 24% and 25% respectively (p=0.66). Conclusions: Despite lower prevalence, there is a disproportionately higher number of metastic and untreated cases of esophageal cancer among Hispanics. This disparity may be explained by Hispanics’ limited access to medical care exacerbated by their socioeconomic and insurance status. Our findings warrant further clinical and epidemiologic research to reveal other factors impacting these health and health care disparities. Research Sponsor: None.
Metachronous remnant gastric cancer after proximal gastrectomy. First Author: Kenichi Ishizu, Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan.

Background: Proximal gastrectomy is frequently selected for early gastric cancer located at the upper third of the stomach. Annual postoperative endoscopy is considered to be useful for the early detection of metachronous remnant gastric cancer (MRGC). Despite that, we sometimes have also encountered cases that are not suitable for endoscopic resection (ER). The aim of this study is to identify the risk factors for the patients who developed MRGC after proximal gastrectomy, received annual endoscopy, but are not eligible for ER (non-ER).

Methods: We retrospectively analyzed 191 patients who had received annual endoscopic surveillance after undergoing PG for cT1 gastric cancer at NCCH between 2006-2015. MRGCs were categorized into two groups: ER group and non-ER group. The remnant stomach was defined as three locations: pseudotrachea (P), stomach and antrum. Results: The median observation period was 73 (range 12-168) months. MRGC was observed in 29 cases with 32 lesions. ER was possible for 20 lesions (ER group, 62.5%), but 12 were not (non-ER group, 37.5%). We compared the characteristics between ER group and non-ER group in terms of sex, age (> 65 years), interval from the initial surgery (> 30 months), the location (P vs non-P), and cross-sectional circumference (posterior wall vs. others). In both univariate and multivariate logistic regression analysis, only the location at P was identified as a risk factor for non-ER group (OR 25.0, 95% CI: 1.8-339, p = 0.015). Among 12 lesions of the non-ER group, the location of P was found in 6 (50%) lesions. As compared with MRGC at the non-P, that at the P (n = 6) was characterized by younger patients (57.5 (range 37-69) vs. 69 (56-77) years), larger size (36 (7-57) mm vs. 9 (9-24) mm), deeper depth (MP or MP vs. 1/6), and frequent nodal metastasis (3/6 vs. 0/6). The interval to detect MRGC appears to be longer in the P (78 (31-96) months) than that at the non-P (60 (31-96) months), but the difference was not statistically significant (p > 0.86). Then, we examined the visibility and the mucosal normality of the area developing MRGC in the annual follow-up endoscopy one year before the detection of MRGC (n = 32). In 25 lesions at the non-P, the visibility and the mucosal normality was secured in 21 (84%), while 5 P lesions were difficult to observe (71.4%, p = 0.01) due to food residues in 4 (57%, p = 0.047) and insufficient expansion of the gastric mucosa in 4 (57%, p = 0.001).

Conclusions: With annual follow-up endoscopy, complete clearance and adequately extending the gastric mucosa could lead to the early detection of MRGC at the P. Research Sponsor: None.

Unveiling proteomic diversity: A quantitative study of antibody drug conjugate and chemotherapy targets in gastroesophageal cancer. First Author: Yusong Chen, Cancer Center, Renmin Hospital of Wuhan University, Wuhan, China.

Background: Gastroesophageal cancer (GEC), is a significant global health concern with a 5-year relative survival of 7% for metastatic GEC. Standard treatments often include surgery, chemotherapy, and radiation therapy, but their effectiveness can be limited. Chemotherapy is frequently utilized in the treatment of GEC, although no biomarkers for chemotherapy are used in the selection of the chemothero agent. There are several well-known biomarkers of resistance and sensitivity for various chemo agents. However, the use of protein expression and the functional activity of cancer biomarkers associated with chemotherapy efficiency in 125 GEC patients. These include resistance markers for platinum agents (ERCC1), and tubulin inhibitors (TUBB3). In addition, we included sensitivity markers for irinotecan/topotecan (Topo1), and doxorubicin/etoposide (Topo2A). We also assessed the presence of the following antibody-drug conjugate markers (EGFR, Her2, Trop2, FR-alpha, Mesothelin, Axl, CLDN18.2, and Nectin-4).

Methods: FFPE tumor tissues from 125 clinical GC patients were microdissected and solubilized for mass spectrometry-based targeted proteomic analysis in our CLIA-certified laboratory. 72 proteins were quantified from 2-3 sections of FFPE tissue. Results: 5-Fuouracil (5-FU), taxanes, and platinum agents (such as carboplatin) are among the chemotherapy agents that are frequently used to treat GEC. TYMP, a sensitivity marker for 5-FU, was expressed in 32% of GEC cases. ERCC1, a resistance marker for platinum drugs, was expressed at 34%. Additionally, 48% of GEC exhibited TUBB3, a resistance marker for paclitaxel and docetaxel. Topoisomerase I (Topo1) is the target for irinotecan or topotecan, and is also the target for some ADCs (e.g. trastuzumab deruxtecan, saczumtuzumab govetec etc.). Topo1 was expressed in 92% of GEC with a 10x range (415 - 4195 amol/μg). Another topoisomerase, Topo2A, targetable by etoposide, epirubicin, and doxorubicin, was expressed in 59% of GEC with 19x range (402-7804 amol/μg). ADC targets, such as EGFR (82% detected with 18x range of distribution), Her2 (18%, 4x), AXL (18%, 7x), MET (27%, 19x), and Trop2 (57x).

Conclusions: Our large-scale proteomic studies have identified a range of potential therapeutic targets across various treatment modalities. Research Sponsor: None.

Natural history of gastric leiomyoma. First Author: Kwangbeom Park, Nowon Eulji Medical Center, Seoul, South Korea.

Background: Most gastric leiomyomas are asymptomatic and benign subepithelial tumors (SETs); however, some may increase in size or become symptomatic. Understanding their natural history is therefore important to their management. We investigated the natural history of histologically proven gastric leiomyomas. Methods: We retrospectively analyzed 191 patients who had undergone annual endoscopic surveillance after undergoing PG for cT1 gastric cancer at NCCH from 2001-2015. The primary end point was presence of lymph node metastasis (LNM), and the secondary outcome was the histopathologic results in cases that underwent resection.

Results: Among the 231 patients with histologically proven gastric leiomyomas, the most frequent location was the cardia (77.1%), and the median size was 3 cm (IQR 2-4 cm). Eighty-four cases were followed up over a median period of 91.3 months. During the follow-up period, tumor size increased in 2 cases (2.4%). Surgical results showed that one case was leiomyoma, and the other was leiomyosarcoma. Among the remaining cases without change in size, 15 underwent surgical resection (n = 10) or endoscopic resection (n = 5), and all cases were confirmed as leiomyoma. Conclusions: Most gastric leiomyomas are benign SETs, and an increase in size is not frequent, even in large-sized cases. Close monitoring with routine follow-up without resection may be sufficient in cases of histologically proven gastric leiomyoma. However, in cases of ulceration or size increase, resection may be beneficial. Research Sponsor: None.

Prediction of lymph node status in stage T1 esophageal squamous cell carcinoma. First Author: Yongshun Chen, Cancer Center, Renmin Hospital of Wuhan University, Wuhan, China.

Background: With the development of endoscopic therapy and the introduction of immunotherapies, it is more important for preserving the esophagus and uninvolved lymph nodes. Lymph node metastasis (LNM) is an important tool for treatment decision making and is a poor prognostic factor for esophageal cancer. Research Sponsor: None.

Methods: We collected patients with T1 ESCC who underwent endoscopic resection or esophagectomy from 2014 to 2021 in three cancer centers. The primary end point was presence of lymph node metastasis (LNM) in surgical resection specimens or detection of metastatic lymph nodes on imaging studies. Statistical analysis was performed using Univariate and multivariate logistic regression with the presence of LNM as the dependent variable and the following variables as independent variables: tumor invasion into the submucosa, poor histological grade, and lymphovascular invasion in the resected tissue samples of T1 ESCC to further supplement the model from the cellular and molecular level, and used 6 markers (CK, CD34, D2-40, CD4, CD8, FOXP3) and DAPI dye to evaluate the generalization of the model. We then prospectively collected 28 surgically resected tissue samples of T1 ESCC to further supplement the model from the cellular and molecular level, and used 6 markers (CK, CD34, D2-40, CD4, CD8, FOXP3) and DAPI dye to process multiple immunofluorescence (mIF) staining. Afterwards, we analyzed the density, spatial distribution of microvessels, lymphatic capillaries and tumor-associated immune cells and the interaction between them and malignant cells in the tumor microenvironment of T1 ESCC to explore the relationship between tumor microenvironment and risk of LNM. Using the function 'lm' constructed the prediction model. The area under the curve (AUC) of receiver operating characteristic and calibration graphs were used to assess the performance of the model. An external validation was conducted to evaluate the generalization of the model. We then prospectively collected 28 surgically resected tissue samples of T1 ESCC to further supplement the model from the cellular and molecular level, and used 6 markers (CK, CD34, D2-40, CD4, CD8, FOXP3) and DAPI dye to process multiple immunofluorescence (mIF) staining. Afterwards, we analyzed the density, spatial distribution of microvessels, lymphatic capillaries and tumor-associated immune cells and the interaction between them and malignant cells in the tumor microenvironment of T1 ESCC to explore the relationship between tumor microenvironment and risk of LNM. Research Sponsor: None.

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Development and application of an ultra-sensitive ctDNA mutation profiling assay in monitoring therapy response and drug resistance. First Author: Tom Zhao, Predicine, Inc., Hayward, CA.

Background: Next-generation sequencing (NGS) assays offer efficient high-throughput profiling methods for analyzing circulating tumor DNA (ctDNA) in blood or other liquid biopsy specimens. The ctDNA mutant allele fractions of patients after treatment is often detected at baseline or only detected in PredicineCARE ULTRA. This assay was then adopted for longitudinal sequencing of 57 serial plasma samples from 6 patients with HER2+ gastroesophageal adenocarcinomas (GEO) who underwent combined treatments (capecitabine, oxaliplatin, bevacizumab, and trastuzumab) at different time points (baseline, response, and progression). Results: PredicineCARE ULTRA ctDNA assay exhibited exceptional sensitivity in calling single nucleotide variants and indels, with a 98.0% detection rate at a LoD of 0.075% mutant allele frequency (MAF) for 60 ng ctDNA. This is significantly lower than the LoD (0.25% MAF) of a standard PredicineCARE ctDNA assay. The ultra-sensitive assay also displayed excellent analytical specificity (99.99%) and precision (intra-assay 100%; inter-assay 99.41%). In 6 GEO patients’ longitudinal samples, PredicineCARE ULTRA ctDNA assay detected additional somatic mutations with the MAFs spanning in a range from 0.024% to 0.1% beyond 124 baseline mutations identified using standard PredicineCARE. In two representative cases presented here, all baseline mutations (genes TP53 and PIK3CA, etc.) were consistently reported in the follow-up time points with a noticeable MAF reduction (lowest MAFs from 0.046% to 0.024%) during response. Subsequent elevations were observed in more genes, including low-frequency mutations (KRAS and ERBB2) not detected at baseline or only detected in PredicineCARE ULTRA. Conclusions: This study demonstrated the clinical utility of the ultra-sensitive ctDNA molecular profiling at 100,000X sequencing depth in treatment selection, therapy monitoring, and drug resistance studies. Research Sponsor: None.

A scoring system for selecting nivolumab or irinotecan in the later-line chemotherapy for advanced gastric cancer: A Japanese multicenter retrospective study. First Author: Yusuke Amanuma, Department of Clinical Trial Promotion, Chiba Cancer Center, Chiba, Japan.

Background: Although Nivolumab (NIVO) or irinotecan (IRI) monotherapy is one of the later-line chemotherapies for the advanced gastric cancer (AGC) patients, there are no prospective data of their comparison, and no indicators for selection of them. Methods: Clinical data of AGC patients treated with NIVO or IRI as later-line were collected from 7 institutions between September 2015 and September 2016. Efficacy of the two treatment groups was compared in the entire cohort and in the propensity score matching cohort. Factors which affect the prognosis were explored by multivariate analyses and the scoring system was developed using Cox regression. Results: In the analysis of entire cohort (317 patients), the median OS was 48 months (95% CI: 3.6–5.8) in the NIVO group and 59 months (95% CI: 4.9–7.2) in the IRI group, and those were 48.0 months (95% CI: 3.6–5.7) and 60.0 months (95% CI: 4.5–7.2) in the analysis of the propensity score matching cohort (248 patients), respectively. There were no differences in OS. We developed a risk score involving 1-Neutrophil to Lymphocyte Ratio (NLR), age, ECOG performance status, peritoneal metastasis, 5-gastroctomy, and 6-liver metastasis to assess potential effect modification. Based on the result, IRI was favored in the higher-risk group (<4 points, with double weight to 2, 3, and 4) for both OS/PFS. In contrast, NIVO was better OS/PFS in the lower-risk group (<1 point). Conclusions: According to the real-world data from multicenter in Japan, NIVO and IRI generally showed equivalent outcomes. The scoring system we explored may be useful for selecting appropriate later-line chemotherapy, either NIVO or IRI. Research Sponsor: None.

Efficacy and safety of trastuzumab deruxtecan and nivolumab as third- or later-line treatment for HER2-positive advanced gastric cancer: A single-institution retrospective study. First Author: Keitaro Shimozaki, Department of Gastrointestinal Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan.

Background: Despite the difficulty of directly comparing trastuzumab deruxtecan (T-DXd) and nivolumab as third- or later-line treatment for HER2-positive advanced gastric cancer (AGC) in randomized trials, discussions regarding optimal treatment strategies are desired. Methods: This single-institution retrospective study aimed to describe the real-world efficacy and safety of T-DXd and nivolumab as third- or later-line treatment for patients with HER2-positive AGC treated between March 2016 and May 2022. Results: Overall, 58 patients (median age, 64 years; 69% male) were eligible (T-DXd group, n = 20; nivolumab group, n = 38). Most had HER2 3+ (72%) and presented with metastatic disease at diagnosis (66%). Response rates in the 41 patients with measurable lesions were 50% and 15% in the T-DXd and nivolumab groups, respectively. The T-DXd and nivolumab groups had a median progression-free survival of 4.8 months (95% confidence interval, 3.3–7.0) and 2.3 months (95% CI, 1.5–3.5), median overall survival of 10.8 months (95% CI, 6.9–23.6) and 11.7 months (95% CI, 7.6–17.1), and grade 3 or greater adverse event rates of 50% and 2%, respectively. Overall, 64% received subsequent treatment. Among 23 patients who received both regimens, the T-DXd–nivolumab and nivolumab–T-DXd groups had a median overall survival of 14.0 months (95% CI, 5.0–not reached) and 19.3 months (95% CI, 9.5–25.1), respectively. Conclusions: T-DXd and nivolumab had distinctive efficacy and toxicity profiles as third- or later-line treatment for HER2-positive AGC. Considering the distinct features of each drug and combination, results may help clinicians select the optimal treatment approaches for patients with HER2-positive AGC. Research Sponsor: None.

Real-world comparison of treatment outcomes between advanced esophagogastric junction adenocarcinoma and gastric adenocarcinoma. First Author: Toru Kadono, Cancer Chemistry Therapy Center, Osaka Medical and Pharmaceutical University, Tottori, Osaka, Japan.

Background: The characteristics of esophagogastric junction adenocarcinoma (EGJA) are different from those of gastric adenocarcinoma (GA). Although chemotherapy for advanced GA has been adapted for advanced EGJA, its efficacy remains unknown. This study aims to elucidate the effectiveness of chemotherapy for advanced EGJA in real-world practice. Methods: This retrospective study compared treatment outcomes between advanced GA and EGJA in patients with performance status (PS) 0 to 2 who received double or triplet chemotherapy, including platinum agents, as first-line treatment at our hospital between 2010 and 2020. Patients with non-curative resection factors limited to poor peritoneal cytology, or who relapsed during adjuvant chemotherapy or within 6 months after its completion, were excluded. Results: Of the total 825 patients, 765 had GA and 60 had EGJA. The baseline characteristics of the GA and EGJA groups were as follows, respectively: median age 65.0 and 59.5 years (p = 0.02); PS 0, 1, and 2 (double weight to 2, 3, and 4) for both OS/PFS. In contrast, NIVO was better OS/PFS in the lower-risk group (<1 point). The proportions of fluoropyrimidine, taxanes, and irinotecan in all treatment lines did not differ between the two groups (fluoropyrimidine, 99.7% vs. 100%; taxanes, 70.1% vs. 73.3%; irinotecan, 23.0% vs. 23.3%). However, the EGJA group used ramucirumab, trastuzumab, and immune checkpoint inhibitors (ICIs) significantly more frequently than the GA group (ramucirumab, 27.8% vs. 43.3%, p = 0.02; trastuzumab, 15.4% vs. 26.7%, p = 0.03; IGS, 21.0% vs. 41.7%, p = 0.01). Overall survival did not differ between the two groups (median, 14.8 months vs. 18.5 months, HR 0.80, 95% CI, 0.59–1.10, p = 0.17). Moreover, multivariate analysis revealed that EGJA and GA had a comparable prognosis (HR 1.23; 95% CI, 0.87-1.72, p = 0.24). HER2 positivity was a prognostic factor in multivariate analysis, whereas diffuse histology, poor PS, lymph node metastasis, liver metastasis, and the presence of peritoneal metastasis were poor prognostic factors. There was no difference in time-to-treatment failure between the two groups for first-line (median, 6.1 vs. 4.9 months, HR 0.96, 95% CI, 0.73-1.28, p = 0.80), second-line (median, 2.9 vs. 3.5 months, HR 0.99, 95% CI, 0.73-1.34, p = 0.93), and third-line treatment (median, 1.9 vs. 2.7 months, HR 0.78, 95% CI, 0.53-1.13, p = 0.62). Conclusions: In real-world practice, the efficacy of chemotherapy for advanced EGJA was comparable to that for advanced GA. Research Sponsor: None.

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Impact of time-of-day on nivolumab monotherapy infusion in patients with metastatic gastric cancer. First Author: Yasunobu Ishizuka, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Background: Nivolumab monotherapy, an immune checkpoint inhibitor, is a standard of care for patients with metastatic gastric cancer (mGC) as a later-line treatment. Several studies have suggested that the circadian rhythm is essential in immune system function, including anti-cancer immunity. This study evaluated whether the time-of-day patterns of nivolumab infusion alter the efficacy of mGC treatment. Methods: This study retrospectively analyzed 298 consecutive mGC patients who received nivolumab monotherapy at a single institution between December 2014 and December 2022. Patients were divided into early (EA)- and late (LA)-nivolumab infusion groups: EA group = <70% of their infusions before 14:00, and LA group = <70% of their infusions before 14:00. Treatment efficacy (overall response rate [ORR], disease control rate [DCR], progression-free survival [PFS], and overall survival [OS]) was evaluated. Multivariate analyses included variables with P values < 0.1 in univariate analyses. Results: A total of 248 patients were eligible; 140 were classified as having EA, and 108 as having LA. Most baseline characteristics were similar between EA and LA. In contrast, the median infusion time was earlier in EA than in LA (11:50 vs. 14:22). The median follow-up time was 9.0 months (range, 1.2–64.7 months). ORR and DCR were significantly higher in the EA than in the LA among 149 patients with measurable lesions (ORR, 16.9% vs. 3.3%, P = 0.01; DCR, 47.2% vs. 20.0%, P < 0.01). Patients with EA had significantly better prognoses than those with LA in terms of PFS (median PFS, 2.3 vs. 1.6 months; hazard ratios [HR], 0.65; P = 0.01) and OS (median OS, 7.6 vs. 3.9 months; HR, 0.64; P = 0.01). EA patients received the subsequent chemotherapy more frequently than those in LA (25% vs. 32%; P = 0.01). Multivariate analyses, including factors such as age, ECOG performance status, histological type, ascites, modified Glasgow Prognostic Score, and timing of nivolumab infusion, showed that EA was an independent prognostic factor for PFS (adjusted HR, 0.66; P = 0.01) and OS (adjusted HR, 0.62; P < 0.01). Conclusions: Our data suggest that efforts to schedule nivolumab infusions before mid-afternoon could be considered in daily practice. Research Sponsor: None.

ESOPHAGEAL AND GASTRIC CANCER

Recurrence-free survival as a surrogate for overall survival in esophageal squamous cell carcinoma: Nationwide real-world data from Japan. First Author: Jun Oku, Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Background: One of the limitations of the established gold standard, overall survival (OS), is that it requires an extended follow-up period. Addressing this challenge involves investigating appropriate statistically and clinically relevant surrogate endpoints. However, there is a paucity of studies using real-world data (RWD) to explore surrogacy in patients with esophageal squamous cell carcinoma (ESCC). Our study aims to investigate whether recurrence-free survival (RFS) is a valid surrogate endpoint for RWD in surgically resectable advanced ESCC patients, utilizing a comprehensive nationwide database in Japan. Methods: The ESCC patients who received neoadjuvant CF (cisplatin and 5-fluorouracil) or DCF (docetaxel, cisplatin and 5-fluorouracil) at 58 Japanese esophageal centers certified by the Japan Esophageal Society were retrospectively reviewed. Kendall's tau between RFS and OS was used at the individual level, and the coefficient of determination was used at the institutional level to assess surrogacy. Additionally, surrogacy between each short-term postoperative endpoint (pathological complete response [pCR] or pathological grade) and OS was investigated using novel statistical methods. Results: Our study encompassed 3154 ESCC patients who underwent subtotal esophagectomy from 2010 to 2015. The cStage I/II/III/IVA/VB (due to supracricovacular lymph node metastasis) was 224 (7.1%), 1008 (32.0%), 1664 (52.8%), 117 (3.7%), and 140 (4.4%), respectively. The 5-year OS and RFS rate for the entire cohort was 56.6% and 47.7%, respectively. In the primary analysis, a strong correlation between RFS and OS was found (Kendall’s tau = 0.797, 95% confidence interval [CI]: 0.782 to 0.812) at the individual level. Subgroup analysis revealed that the better the pathological response, the higher the tau value. An adjusted R² of 100.0% (95% CI: 40.2 to 100.0) was obtained with the meta-regression model at the institutional level. The surrogate threshold effect was 0.703. Tau between pCR or pathological grade and OS were = 0.025 (95% CI: 0.035 to 0.269) and 0.062 (95% CI: 0.006 to 0.209), respectively. Conclusions: The present study was the first nationwide RWD investigation to demonstrate a strong correlation between RFS and OS in surgically resectable ESCC patients who underwent neoadjuvant chemotherapy (NAC). Notably, this correlation was more pronounced in patients who had a more effective response to NAC. These findings hold promise for expediting the development of novel neoadjuvant treatment by shortening the duration of clinical trials. Research Sponsor: None.

Clinical risk factors for splenic hilar nodal metastasis in remnant gastric cancer after distal gastrectomy. First Author: Ryota Sakon, Department of Gastric Surgery, National Cancer Center Hospital East, Kashiwa, Japan

Background: Splenectomy is usually considered to be required for complete dissection of splenic hilar lymph node (node 10 LN) in gastric cancer (GC). Although spleen-preserving D2 dissection has been considered sufficient for the advanced GC not invading the greater curvature based on the JCOG0110 clinical trial, D2 gastrectomy with splenectomy remains the standard procedure for the advanced GC involving greater curvature in Japan. However, the applicability of this treatment for remnant gastric cancer (RCG) is unclear because the lymphatic flow and lymphatic metastatic pattern may have been changed after initial gastrectomy. There are no guidelines for splenic hilar nodal dissection for RGC. In this study we evaluated risk factors for node 10 nodal metastasis in RGC. Methods: This study retrospectively examined RGC patients who received gastrectomy with node 10 nodal dissection after distal gastrectomy at two high-volume cancer centers in Japan between 1998 and 2015. Results: 99 patients were entered in this study. The node 10 nodal metastatic rate was 12.1% (12/99). Initial gastrectomy was performed for benign in 42 patients and for malignant in 52 patients. The median duration from the initial gastrectomy was 20 (1-55) years. Major tumor location was lesser curvature in 46 patients, anterior wall in 11, greater curvature in 19, posterior wall in 11, and the whole in 12. Large type 3 (≥8cm) and type 4 were found in 18 cases. The median tumor size was 50 (10-232) mm. The depth of invasion was cT1 in 31 patients, cT2 in 19, cT3 in 11, cT4a in 28, and cT4b in 10. Histology was differentiated type in 46 patients and undifferentiated type in 56. Completion gastrectomy was performed in 98 patients and partial gastrectomy in 1. 89 patients underwent splenectomy. The univariate analysis showed that tumor location (lesser curvature vs others, p = 0.027) and depth of invasion (cT1-c vs cT4, p = 0.002) were significant risk factors for node 10 nodal metastasis. By multivariate analysis, these two factors remained significant. Metastasis to node 10 nodal metastasis was 0% (0/28) in patients without both risk factors, 11-12% in those with at least one risk factor, and 30% (6/20) in those with both risk factors. Conclusions: The tumors not confined to the lesser curvature and cT4 were significant risk factors for node 10 nodal metastasis of RGC after distal gastrectomy. Splenectomy should be considered for complete splenic hilar nodal dissection when these risk factors are positive. Research Sponsor: None.

Safety and short-term efficacy of adjuvant nivolumab after neoadjuvant docetaxel, cisplatin, and fluorouracil for locally advanced esophageal squamous cell carcinoma. First Author: Mashiro Okunaka, Department of Pharmacy, National Cancer Center Hospital East, Kashiwa, Japan

Background: Efficacy and safety of adjuvant nivolumab has been demonstrated in patients with locally advanced esophageal squamous cell carcinoma (ESCC) in Japan based on the JCOG109 study, the safety and efficacy of adjuvant nivolumab in this population remains unclear. Here, we report the short-term safety and efficacy of adjuvant nivolumab after neoadjuvant DCF in patients with locally advanced ESCC. Methods: We retrospectively reviewed medical records of patients who received adjuvant nivolumab after neoadjuvant DCF and surgery for locally advanced ESCC from Nov 2021 to Jun 2023 at National Cancer Center Hospital East. Pathological stage was classified by UICC-TNM 8th edition. Adverse events were assessed according to CTCAE v5.0. Disease-free survival (DFS) was calculated by Kaplan-Meier method. Results: The study included a total of 33 patients with a median age of 67 years (range, 56-77), of which 29 patients were male. All patients had residual pathological disease, with ypStage I/II/III/IV of 5/11/16/11 patients. Median time from surgery to the initiation of adjuvant nivolumab was 10.6 weeks (range, 7.1-16.4 weeks). Treatment-related adverse events (TRAEs) occurred in 27 patients (82%), with pruritus (n = 13, 39%), rash (n = 7, 21%), hypothyroidism (n = 7, 21%), xerosis (n = 6, 18%), diarrhea (n = 5, 15%), hypopituitarism (n = 5, 15%), pneumonitis (n = 1, 3%), and hepatic dysfunction (n = 1, 3%). Among these TRAEs, one patient developed grade 3 of hepatic dysfunction, which resolved with corticosteroid. TRAEs which led to discontinuation of nivolumab were hepatic dysfunction (n = 1, 3%), diarrhea (n = 1, 3%), and pneumonitis (n = 1, 3%). No treatment-related death was observed. With a median follow-up of 10.3 months, 1-year DFS rate was 63.3% (95% CI, 39.8-79.7%). Among 9 patients who experienced recurrence (locoregional, n = 3, distant, n = 6), 8 patients received subsequent therapy, including systemic chemotherapy, Salvage chemotherapy (n = 3). Conclusions: The safety and short-term efficacy of adjuvant nivolumab after neoadjuvant DCF and surgery was comparable to the results of the CheckMate-577 trial. Our study suggests that adjuvant nivolumab might be a possible treatment option in patients with locally advanced ESCC patients with residual pathological disease after neoadjuvant DCF followed by surgery. Research Sponsor: None.

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Correlation between histopathological response by neoadjuvant DCF therapy and the clinical efficacy of palliative platinum-containing regimens for recurrent ESCC. First Author: Shota Igaue, Department of Esophageal Surgery, National Cancer Center Hospital, Tokyo, Japan

Background: Docetaxel and cisplatin, 5-FU (DCF) chemotherapy has established as the standard neoadjuvant treatment for resectable locally advanced esophageal squamous cell carcinoma (ESCC) based on the results of the JCOG1109 study. If patients showed recurrence of ESCC after neoadjuvant DCF therapy, platinum-containing regimens were used as palliative treatment in the clinical practice. However, there were no data of correlation between histopathological response by neoadjuvant DCF therapy and clinical efficacy of palliative platinum-containing regimens for recurrent ESCC. Methods: We retrospectively reviewed patients with ESCC who received neoadjuvant DCF therapy and R0 resection between Feb 2014 to June 2022 in our hospital. We evaluated histopathological response by DCF (40% [95% CI]: 23%–29%) and clinical efficacy response by DCF using Fisher’s exact test and the log-rank test. In addition, we analyzed clinical factors related to clinical efficacy of palliative chemotherapy using Cox proportional hazards models. Results: In this study, 398 patients received neoadjuvant DCF therapy and we identified 88 eligible patients with recurrence. Among 88 patients, 33 patients initially received palliative chemotherapy and analyzed. Patients’ characteristics were followed 1.2 (0.6–2.1) years, median age 62 (53–72) years, PS 0/1/2: 1 2 (36.4%)/1 7 (51.5%), 4 (12.1%). Histopathological response 0/1/2/3 in 1 (3.0%)/23 (63.7%)/17 (43.0%/2 (6.1%) patients, respectively. Among these 33 patients, 23 patients received platinum-containing regimens. In the patients who received palliative chemotherapy, the ORR were 34.8% (8/23) in histopathological response 0/1/2/3 group, respectively. Among 23 patients having histopathological response 2/3 group, with no statistical difference (p = 0.696). The median PFS was 2.43 (95% CI: 2.33–2.53) months in histopathological response 0/1 group and 4.04 (95% CI: 0.07–10.77) months in histopathological response 2/3 group (HR [95% CI]: 1.121 [0.413–3.043]. Multivariate analysis using Cox proportional hazards models revealed chemotherapy-free interval (CFI) < 6 months (HR [95% CI]: 3.394 [1.795–6.452]) was the independent prognostic factor. Histopathological response did not show the significance (HR [95% CI]: 0.723 [0.195–2.678]). Conclusions: Histopathological response by neoadjuvant DCF therapy did not affect the efficacy of platinum-containing regimens for recurrent ESCC, while CFI might be the independent prognostic factor. Research Sponsor: None.

Real-world experience with trastuzumab deruxtecan among patients with gastric cancer: 4-month interim analysis of an all-patient post-marketing surveillance study in Japan. First Author: Hisato Kawakami, Kindai University Faculty of Medicine, Osaka-Sayama, Japan

Background: Intestinal lung disease (ILD) is an important identified risk in the Japanese risk management plan of trastuzumab deruxtecan (T-DXd). In Japan, all-patient post-marketing surveillance (PMS) is underway to investigate the risk of ILD among patients with gastric cancer treated with T-DXd in a real-world setting. We present an interim analysis of the large-scale all-patient PMS (J-TRG2000020001) with an observation period of 12 months that enrolled all patients treated with T-DXd for HER2-positive unresectable advanced or recurrent gastric cancer between Sep 2020 and Dec 2021. This interim analysis is based on safety data from the first 4 months of all enrolled patients. All potential ILD (identified based on the pre-specified list of AE terms) reported by physicians were adjudicated by an independent ILD adjudication committee (ILD-AC). The incidence of ILD was calculated from adjudicated drug-related ILD. Results: The interim analysis set included 1074 patients with median age of 70 years (range: 23-100). Of the 1074 patients, 1051 (97.9%) received T-DXd as third-line or later treatment. One hundred and eight patients (10.1%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) 2 or greater, and 32 (3.0%), 3 (0.3%), and 23 (2.1%) patients had severe renal impairment (15%: creatinine clearance (CL) <30 mL/min), end-stage renal disease (CL <15 mL/min), and ILD/radiation pneumonitis at baseline, respectively (all of which were defined as exclusion criteria in clinical trials of T-DXd). Median initial dose of T-DXd was 6.4 mg/kg (range: 3.1-6.4). Median treatment duration of T-DXd was 4.0 months (range: 0.7-6.0). During the first 4 months from the initial treatment, T-DXd was discontinued in 272 (25.4%) patients with adjudicated drug-related ILD were 5.2% (56/1074), 1.5% (16/1074) and 0.7% (7/1074), respectively. Of the 56 patients with adjudicated drug-related ILD, 54 (96.4%) discontinued T-DXd. The incidence of adjudicated drug-related ILD by time from initial treatment of T-DXd was 0.7% (7/1074) at ≥1 month, 2.0% (19/949) at ≥2 months, 2.7% (22/829) at ≥3 months, and 3.5% (36/1036) at ≥4 months. The interim analysis revealed patient experiences and treatment profiles of T-DXd and the incidence of ILD during the first 4 months since initial treatment in a real-world setting in Japan. The final analysis including a risk factor analysis for ILD of the ongoing PMS is planned. Research Sponsor: Daiichi Sankyo Co., Ltd.

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Assessment of circulating tumor DNA (ctDNA) burden and association with outcomes in metastatic gastric cancer (mGC) patients using real-world data (RWD). First Author: Senaka A. Peter, Merck & Co., Inc., Rahway, NJ

Background: ctDNA burden has been shown to have potential uses in early cancer detection, guiding treatment decisions, residual disease and drug resistance detection, and response monitoring. While published literature suggested that ctDNA may be prognostic of clinical outcomes for various tumor types, there is limited RWD assessing its use in mGC. This study uses RWD to evaluate the association of pre-treatment ctDNA burden with clinical outcomes in mGC. Methods: Patients were identified from the Guardant INFORM real-world clinical-genomic database, which links ctDNA results via plasma-based next-generation sequencing Guardant360 assay (G360) to de-identified claims data. Adult mGC patients in the US, who underwent esophagectomy or first-line treatments prior to September 1, 2012 and underwent testing with G360 from June 2014 to March 2022 were included. For those who received first-line (1L) therapy within 60 days after a G360 test result, median of the maximum variant allele fraction (mVAF) was used to classify them into high or low ctDNA burden groups, with undetectable ctDNA burden considered low. Associations with time to next treatment (TTNT) and overall survival (OS) were assessed using log rank tests and multivariable Cox proportion hazards models adjusting for age, sex, Elixhauser comorbidity score, and anatomical location. Results: 2,200 mGC patients were identified, of which 824 (37%) initiated 1L therapy within 60 days after a G360 test. Among the 824 patients, mean age was 63 years, 70% were male and 47% had gastric adenocarcinoma and 53% gastroesophageal junction cancer. Median mVAF among these patients was 2.9%, with 91% having detectable ctDNA. Patients with high ctDNA burden treated with 1L chemotherapy (Chemo) showed significantly worse TTNT and OS than low ctDNA burden patients (Median TTNT 4.7 months vs 7.5 months, p<0.001; Median OS 14.2 months vs 24.7 months, p<0.001). Multivariable Cox analyses showed similar results for 1L Chemo group. Treatment group outcomes based on adjusted Cox models were reported (Table). Conclusions: We used RWD to demonstrate that high pre-treatment ctDNA burden was associated with worse clinical outcomes in a mGC population treated with 1L Chemo. Our analysis, together with the body of evidence that suggest ctDNA burden could be used as a prognostic biomarker for mGC. The small sample size of the other 1L treatment groups warrants further investigation because the use of 10-based therapy is expected to increase with recent approvals. Research Sponsor: None.

<table>
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<th>P value</th>
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Chemo=chemotherapy, IDO=immunotherapy, HR= hazard ratio. *Hazard ratios compare ctDNA high vs ctDNA low (reference).

Ten-year overall survival of localized lower thoracic and esophagogastric junction carcinoma receiving trimodality therapy: A National Cancer Database analysis. First Author: Hanna Kakish, University Hospitals Cleveland Medical Center, Cleveland, OH

Background: Trimodality therapy, consisting of chemotherpay and radiation followed by esophagectomy, represents the prevailing standard of care for most patients with localized lower thoracic and esophagogastric junction (EGJ) carcinoma. However, robust data reporting the survival of this patient population in the real-world setting is lacking. The primary objective of the current study was to comprehensively analyze the long-term survival of this patient population receiving treatment in a real-world setting and identify factors that significantly influence the survival. Methods: We identified adult patients in the National Cancer Database with localized (cT1NMO or cT2N+M0) lower thoracic or EGJ adenocarcinoma (AC) or squamous cell carcinoma (SCC) receiving trimodality therapy between 2004 and 2020 with multi-agent chemotherapy and ≥ 4139 cGy of radiation followed by esophagectomy. The primary endpoint of the analysis was overall survival (OS), estimated using the Kaplan-Meier method. The impact of clinical, demographic and diagnostic features on OS was determined using the log-rank test. We performed a multivariable (MV) Cox analysis to evaluate the independent association of clinical and demographic variables on OS (data presented as hazard ratio [HR] and 95% Confidence Interval [CI]). Results: The analysis included 21,965 patients, characterized by a median age of 63 years, predominance of males (89.5%), non-Hispanic white patients (89.4%), and AC histology (93.6%). Most patients had T2/T3 tumors (87.3%) and a median age of 63 years (1.17, 1.11-1.22); male gender (1.13, 1.08-1.19); histology, AC vs SCC (1.19, 1.10-1.28); T4 vs T1-T3 tumor stage (1.20, 1.07-1.34); lymph node involvement (1.22, 1.18-1.27); Charlson-Deyo score ≥ 2 (1.23, 1.15-1.32); uninsured or private insurance (1.20, 1.05-1.36); and low-volumecenter (0.8, 0.71-0.98). Further, post-diagnostic testing after 2013-2019 had modestly improved OS (0.87, 0.84-0.90), perhaps reflecting the impact of the CROSS trial published in 2012. Conclusions: This study illustrates the grim long-term survival of patients with localized lower thoracic and EGJ cancer undergoing standard trimodality therapy, underscoring the urgent necessity for innovative therapeutic approaches for this patient group. The improvement in OS following the publication of the CROSS trial was modest. Research Sponsor: None.

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First-line FOLFOX therapy for advanced esophageal squamous cell carcinoma: Multicenter prospective study in Japan. First Author: Kunhiro Fushiki, Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan.

Background: Cisplatin (DDP) plus fluoropyrimidine was the standard first-line treatment in patients with advanced esophageal squamous cell carcinoma (ESCC). FOLFOX is promising option especially in patients with ESCC intolerant to CDDP but there were limited data on efficacy and safety of FOLFOX. We conducted a multicenter prospective observational study of FOLFOX for Japanese patients with ESCC intolerant to CDDP. Methods: Eligible patients had clinical stage IV ESCC, with measurable disease. Eastern Cooperative Oncology Group (ECOG) performance status 0–2, intolerant to CDDP, but tolerable to FOLFOX. FOLFOX (oxaliplatin 85 mg/m², leucovorin 200 mg/m², bolus fluorouracil 400 mg/m², and infusional fluorouracil 2400 mg/m²) was administered every 14 days. The primary endpoint was the response rate (RR) by RECIST v1.1 and the null hypothesis of RR was 10%. Based on the assumption of performing a one-sided test with an α of 0.10, 29 patients were needed to ensure the statistical power of 90% assuming RR of 30%.

Results: In this study, 31 patients were enrolled from 14 hospitals between Apr. 2021, and Jul. 2022 and 30 patients received FOLFOX. The patient characteristics were: median age, 77 (range 66–89) years; male/female, 30/1; ECOG PS 0/1/2, 16/12/3; median creatinine clearance, 49.9 ml/min (33.4–80.2); median G8 score, 12 (range 7–17); and median CARG score, 8 (range 6–13). As the data cutoff of Jul 2023, all 30 patients discontinued FOLFOX. The reason for treatment discontinuation was disease progression, 86.7%; adverse events, 13.3%. Median follow-up time (interquartile range: IQR) was 20.2 (IQR 13.7–23.1) months. Median number of cycles administered were 5 (range 1–24). The RR was 22.6% (95% CI 0.13–0.32; p = 0.001) and disease control rate was 42.6%. Median progression-free survival was 3.9 months (95% CI 2.3–6.1). Median overall survival was 13.3 months (95% CI 9.5–not reached). The incidence of grade 3 or higher adverse events was 40% (neutropenia 26.7%, anemia 3.3%, nausea 6.7%, anorexia 6.7%, infection 6.7%, peripheral sensory neuropathy 3.3%). The RR was achieved in 11 (73%) patients and the disease control rate in 23 (76.7%) patients. Twenty-three patients (76.7%) received subdisease control rate was 42.0%. Median progression-free survival was 3.9 months (95% CI 2.3–6.1). Twenty-three patients (76.7%) received submedian progression-free survival (PFS) (20.3 vs 5.1 months; p < 0.001) and a prolonged median overall survival (OS) (33.4 vs 11.7 months; p < 0.001). In the surgery group, 24 (96%) of 25 patients were performed laparoscopic gastrectomy radical laparoscopic gastrectomy after surgery. There were no deaths during surgery, no lymph node dissection (only one patient underwent open gastrectomy), and 6 (9%) patients achieved complete resection (cR0). The RR in the surgery group was 63% (15/24 patients) and median PFS was 20.3 months (95% CI 16.3–24.6).

Conclusions: FOLFOX is promising therapy for patients with advanced esophageal squamous cell carcinoma (ESCC). The RR was 22.6% (95% CI 0.13–0.32; p = 0.001) and 30.3% (80% CI 0.13–0.32; p = 0.001). Based on the assumption of performing a one-sided test with an α of 0.10, 29 patients were needed to ensure the statistical power of 90% assuming RR of 30%.

Clinical outcomes of conversion surgery following immune checkpoint inhibitors and chemotherapy in stage IV gastric cancer with peritoneal metastasis: First Author: Huayuan Liang, Department of General Surgery, Nanfang Hospital, The First School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, China.

Background: Although anti-PD-1 antibody in combination with chemotherapy and/or targeted therapy has shown promising antitumor activity in advanced gastric adenocarcinoma (GC), the evidence of conversion therapy for initially GC with peritoneal metastasis is limited. This study aimed to clarify the clinical outcomes of conversion therapy for such patients. Methods: In this retrospective single institution cohort study, we analyzed 83 GC patients with peritoneal metastasis who received first-line anti-PD-1 antibody and chemotherapy and/or targeted therapy (trastuzumab) between November 2019 and June 2023. In this retrospective analysis, we found that almost all patients achieved stable disease and/or partial response during the treatment, when preoperative imaging studies, multidisciplinary team discussions, and staged laparoscopy indicated the absence of peritoneal metastasis and the possibility of R0 resection, patients were offered conversion surgery. In this study, palliative surgery was not included. Patients were divided into two groups: conversion therapy group and palliative therapy group. Results: All patients underwent staging laparoscopy at their initial visit and underwent at least 2 treatment cycle, with a median follow-up time of 20.3 (16-24.6) months. Of the 83 patients, 32 patients presented a clinical response and underwent re-laparoscopy. Negative peritoneal metastasis and peritoneal cytology were confirmed in 25 patients who proceeded to undergo the conversion surgery. Compared with palliative therapy group, surgery group had a significantly better median progression-free survival (PFS) (20.3 vs 5.1 months; p < 0.001) and a prolonged median overall survival (OS) (33.4 vs 11.7 months; p < 0.001). In the surgery group, 24 (96%) of 25 patients were performed laparoscopic gastrectomy radical laparoscopic gastrectomy after surgery. There were no deaths during surgery, no lymph node dissection (only one patient underwent open gastrectomy), and 6 (9%) patients achieved complete resection (cR0). The RR in the surgery group was 63% (15/24 patients) and median PFS was 20.3 months (95% CI 16.3–24.6).

Conclusions: Conversion surgery following first-line anti-PD-1 antibody in combination with chemotherapy and/or targeted therapy represented a promising treatment strategy for GC patients with peritoneal metastasis. When immunochemootherapy is effective, active second-look staging laparoscopy should be performed to clarify the possibility of conversion surgery. Research Sponsor: None.
Short-term and long-term results of robot-assisted esophagectomy in cT3br/T4b esophageal cancer at initial diagnosis: Comparison with conventional thoracoscopic surgery. First Author: Takeo Fujita, Division of Esophageal Surgery, National Cancer Center Hospital East, Kashiwa, Japan

Background: Conversion surgery in patients with locally advanced esophageal cancer that is not resectable at first time and has responded to prior therapy remains unclear. Recently, the usefulness of RAME for locally advanced esophageal cancer has begun to be discussed. In this study, we first analyzed the short- and long-term results of RAME, then examined the results of conversion RAME in T3br/T4b patients, and compared them with those of conversion using conventional MIE. Methods: Short-term and long-term postoperative outcomes were analyzed in 203 cases of robot-assisted esophageal cancer resection between 2020/1 and 2023/08. In addition, 33 patients with T3br/T4b who were initially diagnosed with cT3br/T4b and who underwent RAME after prior treatment were selected and compared to 48 cT3br/T4b cases with conversion performed at the same time. Results: The mean age of patients was 65.2 years, male to female ratio 170:33, preoperative treatment including NAC 150.53, and Clinical Stage I/II/III/IV 41:27:97:38. Surgical outcomes included thoracic surgery time of 200.3 min and total blood loss of 154.4 ml. Perioperative outcomes were Clavien-Dindo Grade 1 or higher: suture failure 4.4%, pneumonia 13.3%, and recurrent nerve palsy 16.7%. Long-term prognostic analysis (MST: 483.6days) showed OS 97.29±6.94/80.3/70.9%/3.9%/0.7%/0.5%/0.2%/0.4%/0.8%/2.6%/6.2%/5.2%/4.2% in cStage I/II/III/IV. Especially in cStage I-II/III patients, OS: 81.5%, 3YDFS: 71.4%. Long-term outcomes were not significantly different from those of conventional thoracoscopic procedures performed at the same time. Perioperative outcomes in cT3br/T4b at initial presentation were pneumonia: 16.1%, recurrent nerve palsy rate: 12.1% (excluding complicated resection cases), and these cOS:66.2%/3YDFS:48.7%. The OS:52.7%/3YDFS:40.3% of cT3br/T4b cases in the usual MIE showed a favorable trend in RAME (p=0.002). Of the 38 patients with recurrence after RAME surgery, 19 were local/regional and 19 were distant. Of these, 5/6/5/3 were brain/lung/liver/LN others as the first site of distant metastasis. Conclusions: The short- and long-term results of RAME in our department, including T3br/T4, were described, and the short-term and long-term results of RAME were considered acceptable. In terms of recurrence, local/regional disease control was considered to be relatively good. Research Sponsor: None.

Health-related quality of life (HRQOL) with pembrolizumab (pembro) plus trastuzumab (trast) and chemotherapy (chemo) in first-line HER2-positive (HER2+) advanced gastric cancer: KEYNOTE-811 trial results. First Author: Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: In the phase 3 KEYNOTE-811 study (NCT03615326), first-line (1L) pembrolizumab (pembro) plus trastuzumab (trast) and chemotherapy (chemo) was compared with first-line (1L) chemotherapy (chemo). Objective: The primary objective of this study was to assess the overall survival (OS). End points were least squares mean (LSM) change from baseline, time to deterioration (TTD), and overall improvement/stability rate in prespecified subscales of EORTC QLQ-C30, QLQ-STO22, and QLQ-STO22, EuroQol EQ-5D-5L. LSM changes from baseline were analyzed at wk 24 when pre specified completion and compliance rates of ≥60% and 80%, respectively, were met, based on review of blinded data. Results: In the PRO analyses, 685 pts were evaluable (345 pembrol with trast + chemo, 340 pbo with trast + chemo). Median time from randomization to data cutoff (May 25, 2022) was 24.8 mo (range, 9.3-42.6). Completion rates were >92% at baseline and ~55% at wk 24 for all assessments in both arms. Similar changes in PRO scores from baseline to wk 24 were observed for the pembro vs pbo arms (Table). Similar percentages of pts in each arm had improved or stable scores for the EORTC QLQ-C30 GHS/QOL and physical functioning scales and QLQ-C30 nausea/vomiting subscale and QLQ-C30 appetite loss subscale. Overall improvement/stability rate in prespecified subscales of EORTC QLQ-C30, QLQ-STO22, and EuroQol EQ-5D-5L was 19.9% over the entire course of treatment. Conclusion: New findings from this study include the results of PRO assessment. The improvement in HRQOL with pembrolizumab plus trastuzumab and chemotherapy compared to chemotherapy alone is promising and encourages further research in this population. Research Sponsor: none.

ESOPHAGEAL AND GASTRIC CANCER
Tislelizumab (TIS) plus chemotherapy (Chemo) vs placebo (PBO) plus chemo as first-line (1L) treatment of advanced gastric or gastroesophageal junction adenocarcinoma (GE/JC). Health-related quality of life (HRQoL) outcomes in the RATIONALE-305 study. First Author: Marcia Cruz-Correa, University of Porto Rico, School of Medicine, San Juan, Puerto Rico

**Background:** RATIONALE-305 (NCT03777657), demonstrated statistically significant and clinically meaningful improvements in overall survival (OS) with TIS + chemo (n=501) over PBO + chemo (n=496) as 1L treatment in patients (pts) with advanced GE/JC. This analysis examined HRQoL outcomes of the RATIONALE-305 305 study at final analysis. Methods: Adults with previously untreated, untestable, or metastatic GC/GEJC, were randomized (1:1) to TIS 200 mg or PBO IV once every 3 weeks plus investigator-choice of chemo. HRQoL was assessed using EORTC QLQ-C30 and the STO22-0222d. A fixed mixed model for repeated measures using PBO endpoints at clinical Cycles 4 and 6 was performed. Time to deterioration was examined. Results: TIS + chemo had improved outcomes than PBO + chemo (Table) as indicated by least-squares mean change from baseline to Cycle 6 for QLQ-C30/GHS/QOL (2.52 [95% CI:0.29 to 4.73]), functional (2.46 [95% CI: 0.49 to 4.43]), fatigue (-3.01 [95% CI: -5.78 to -0.24]), and the STO22 index score (1.62 [95% CI: -3.12 to 0.13]), as well as maintaining better gastrointestinal (GI) symptoms (-1.74 [95% CI: -3.55 to 0.06]) and pain (1.18 [95% CI: -4.03 to 2.47]). Pts receiving TIS + chemo had a lower risk for deterioration of QLQ/C30 (0.77 [95% CI: 0.60 to 0.98]), functional (0.72 [0.57 to 0.92]), STO22 index score (0.64 [0.45 to 0.82]), pain/discomfort, and upper GI symptoms. These results, along with prolonging of OS and other secondary efficacy endpoints, as well as a tolerable safety profile, support the benefit of TIS + chemo as a potential 1L treatment option for GC/GEJC. Clinical trial-international: NCT03777657. Research Sponsor: BeGene.
The effects of pre-existing psychiatric disorders on gastric cancer survival. First Author: Josephine Soddano, Department of Medicine, Columbia University Irving Medical Center, New York, NY

Background: Despite advances in available treatment, gastric cancer (GC) survival remains low (34.5% overall 5-year survival). In patients diagnosed with cancer, having a prior psychiatric disorder (PD) has been associated with worse survival outcomes compared with no prior PD. Therefore, we examined the relationship between a prior PD diagnosis and GC survival in the real-world (RW) setting. We queried the Surveillance, Epidemiology and End Results (SEER)-Medicare database from 2000 to 2017 for patients who were 66 years of age or older with histologically confirmed GC. Patients with prior cancer history, who were diagnosed by autopsy or death certificate, or were not continuously enrolled in Medicare for at least one year prior to GC diagnosis were excluded. Patients diagnosed with a PD at least one year prior to GC diagnosis and patients without a prior PD were defined as the exposed and unexposed groups, respectively. PDs were categorized as either mild (depression and anxiety) or severe (bipolar or psychotic disorders and schizophrenia). We performed adjusted multivariable Cox proportional hazards regression modeling to evaluate the relationship between prior PD and 5-year overall and cancer-specific survival. Cancer stage, histologic grade, age at diagnosis, sex, race and ethnicity, rural/urban, comorbidity, socioeconomic status, and marital status were examined as potential confounders. Results: Out of 10,464 identified GC patients, 1,651 had a prior PD (46.3% male, mean age 77.5 years) and 8,813 did not have a prior PD (61.5% male, mean age 77.4 years). Our PD patient cohort included 1,355 mild and 296 severe PD patients. When we examined overall survival, patients with a prior PD had a greater hazard of death compared to patients without a prior PD (adjusted hazard ratio: 1.12; 95% CI: [1.05, 1.19]). However, we found no association between having a prior PD compared with not having a prior PD on GC-specific survival (adjusted hazard ratio: 1.07; 95% CI: [0.99, 1.15]). In GC patients with a prior PD, we examined the effects of severe PD versus mild PD on survival. For overall survival, severe PD patients had a greater hazard of death compared with mild PD patients (adjusted hazard ratio: 1.49; 95% CI: [1.23, 1.65]). Similarly, for GC-specific survival, severe PD patients had a greater death compared with mild PD patients adjusted hazard ratio: 1.26; 95% CI: [1.06, 1.50]). Conclusions: Our study found that GC patients with a prior PD had a greater likelihood of overall mortality compared with GC patients without a prior PD. Our analysis also showed that GC patients with a prior PD were 1.6 times more likely to die from cancer compared with GC patients with a prior mild PD. Future work to identify the mechanism between PDs and cancer survival is critical to develop effective targeted interventions to improve survival of this highly fatal cancer. Research Sponsor: NCI U01 CA 265729.

Real-world (RW) effectiveness of nivolumab plus chemotherapy (NIVO+chemo) in patients (pts) with advanced or metastatic gastric carcinoma, gastroesophageal junction carcinoma, or esophageal adenocarcinoma (GC/GEJC/EAC). First Author: Ian Chau, The Royal Marsden NHS Foundation Trust, London, United Kingdom.

Background: In the CheckMate 649 trial, NIVO+chemo demonstrated superior efficacy vs chemo alone in pts with previously untreated advanced GC/GEJC/EAC (NCT02872116). Research Sponsor: Bristol Myers Squibb.

Patients from the Checkmate 649 trial treated advanced GC/GEJC/EAC in the RW setting. A trend toward OS benefit was previously reported on an abstract. The current study aimed to further evaluate OS and other outcomes in the real-world setting. Real-world datasets were from 33 cancer centers in the US, Japan, France, England, and Spain. In total, 528 pts were eligible for the analysis (231 n = 231) treated with NIVO+chemo and 297 n = 297 treated with chemo. Kaplan-Meier estimates of OS in CPS subgroups. Median follow-up (interquartile range) was 6.0 (2.9–9.0) mo for NIVO+chemo and 6.1 (2.5–9.7) mo for chemo. There were 87 (37.7%) deaths in the NIVO+chemo cohort and 138 (46.5%) in the chemo cohort. NIVO+chemo demonstrated superior overall survival (OS) in the overall cohort, with a 12-mo OS rate of 53.3% and 38.1% for chemo alone with a 2.6-mo improvement in median OS (12.6% 95% confidence interval [CI], 10.2–17.0) mo vs 10.8 (9.1–11.5) mo, P = 0.047. Univariate Cox regression analysis of OS yielded a hazard ratio (HR) of 0.76 (95% CI, 0.58–0.98; P = 0.033) for NIVO+chemo vs chemo alone (95% CI, 0.58–0.98; P = 0.033) for NIVO+chemo vs chemo alone. There was also a consistent trend toward OS benefit in all CPS subgroups (Table). Multivariate analysis of two subgroups yielded a HR of 0.51 (95% CI, 0.30–0.89) for NIVO+chemo vs chemo but was not feasible in other subgroups due to sample size. Conclusions: NIVO+chemo showed superior OS vs chemo alone in previously untreated pts with advanced GC/GEJC/EAC in the RW setting. A trend toward OS benefit was also observed in all CPS subgroups, which will be further examined in future analyses with larger samples and longer follow-up. Clinical trial information: NCT02782116. Research Sponsor: Bristol Myers Squibb.

Association of intensifying supportive care with improved survival in patients with gastric cancer with malignant ascites. First Author: John D Karalis, UT Southwestern Medical Center, Dallas, TX

Background: Gastric cancer patients with malignant ascites often have poor functional status and malnutrition that precludes receipt of systemic therapies. Thus, these patients have a very poor prognosis. Beginning in 2019, our multidisciplinary gastric cancer disease-oriented team implemented a more aggressive supportive care plan for gastric cancer patients with malignant ascites. The initiative included measures such as supplemental enteral nutrition, ascites drainage, and initiation of chemotherapy on an inpatient basis. We compared outcomes for gastric cancer patients who presented with synchronous malignant ascites treated before and after the implementation of the care plan. Methods: We performed a retrospective review of our institutional database to identify patients diagnosed with gastric adenocarcinoma and synchronous malignant ascites between 2010-2012. We compared survival between patients diagnosed from 2010-2018, we will be referred to as the historical control era and patients diagnosed from 2019-2022, which will be called the aggressive supportive care era. Results: 54 patients were included in our analysis; 31 patients were treated in the historical control time frame and 23 patients treated during the aggressive supportive care era. De- mographic, clinical, and pathologic characteristics were similar between groups. 3% of historical controls received supplemental tube feeds at diagnosis as compared to 90% of the aggressive supportive care cohort (p = 0.008). 3% of historical controls received their first cycle of chemotherapy in the inpatient setting versus 30% of patients treated during the aggressive supportive care era (p = 0.001). The median number of chemotherapy cycles received was 5 among historical controls and 9.5 among aggressive supportive care era patients (p = 0.02). There was no difference in the number of days spent as an inpatient between the two groups. The median overall survival for historical control patients was 5.4 months as compared to 10.4 months for patients treated during aggressive supportive care era (p = 0.035). Conclusions: Gastric cancer patients with synchronous malignant ascites treated during a timeframe when our multidisciplinary team implemented more aggressive supportive care measures had improved OS as compared to historic controls. Our results suggest that aggressive supportive measures for these patients with highly challenging clinical issues and poor prognosis can prolong survival. Specifically, initiation of chemotherapy in the inpatient setting and supplemental nutrition should be considered for patients at high risk for treatment intolerance. Research Sponsor: Burroughs Wellcome Fund, 1018897.
Does routine clinical assessment of older adults with gastroesophageal cancer tell the whole story? First Author: Meghan Connors, Fox Chase Cancer Center, Philadelphia, PA

**Background:** Geriatric Assessment (GA) can help oncologists determine fitness of their older patients (pt) for anti-cancer therapy. Our objective was to compare routine provider assessment (PA) and GA of older adults with gastroesophageal cancer (GEC).

**Methods:** Patients ≥65 with any stage of GEC completed a GA. The pt’s provider completed a PA and abnormalities detected by both assessments were centrally reviewed and compared. GA and PA assessed functional status, nutrition, comorbidities, psychological distress, cognition, social support, and chemotherapy toxicity risk. Validated assessment tools were used for the GA. Data collected 3 months post-enrollment included hospitalization, ≥ grade 3 toxicities, and treatment delays. We compared the proportions detected by GA and PA for even fit, healthy patients. providers were blinded to the GA to prevent bias in the PA as a function of the GA.

**Results:** 82 pts were enrolled, majority male (74%), median age 73 (65-91), stage III/IV (82%) disease on first line therapy (79%). Cancer sites included gastric (32%), esophageal (43%), GEJ (26%). Pts demographic and clinical characteristics did not predict for the identification of GA abnormalities. GA detected 196 abnormalities and PA detected 86. Majority of pts (84%) had ≥1 unidentified abnormality by PA. Providers identified more pts with clinically significant comorbidities as compared to GA. However, the GA identified more abnormalities compared to PA in all other evaluated domains (Table). Low agreement was found between PA and GA in any of the domains. Pts scoring high on the CARG chemotherapy toxicity prediction tool (p<0.004) and pts with evidence of psychological distress (p<0.049) had more ≥ grade 3 toxicity. Pts with abnormalities in functional status, nutrition, psychological distress, and a high CARG score were more likely to be hospitalized during therapy. **Conclusions:** Clinical characteristics of older pts with GEC are not predictive of GA abnormalities. While providers were better at identifying comorbidities, the GA resulted in a comprehensive evaluation of all domains and identified significant abnormalities that affect treatment outcomes in this population. Research Sponsor: NCCN - National Comprehensive Cancer Network; NCCN/Lilly 3272101.

**Domains N=82**

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Surgical decision making in locally advanced esophageal adenocarcinoma. First Author: Van Christian Sanderfer, Levine Cancer Institute, Atrium Health, Charlotte, NC

**Background:** Trimodality therapy consisting of chemoradiation followed by surgery (CRT+S) is considered optimal therapy for locally advanced adenocarcinoma (ACA) of the esophagus, yet the morbidity of surgery is substantial. We used CT-derived body composition to identify a high-risk subgroup of patients whose risk of surgery may outweigh the benefit, particularly in patients ≥75 years. 90-day postoperative mortality for the high risk group in the CRT+S group was 25.6% compared to 17.7% in the CRT group.

**Methods:** A total of 396 patients undergoing minimally invasive esophagectomy between 2010 and 2022 were identified. Preoperative CT scans at the L3 vertebral level were analyzed to calculate skeletal muscle mass (SMG) as the product of skeletal muscle area and skeletal muscle density. Logistic regression models were used to evaluate the association of age and SMG with 90-day surgical mortality. Patients were classified based on their predicted probability of 90 day mortality into low and high risk groups, where high risk was defined as the highest-risk 25% of patients. This model was then applied to the study cohort of patients with ACA.

**Results:** Of 316 patients with locally advanced ACA treated with CRT, 254 underwent surgery (CRT+S). 90-day postoperative mortality in the CRT+S group was 5.1%. 74 patients were categorized as high-risk and 242 as low-risk. Among low-risk patients, 213 (88.0%) were treated with surgery (CRT+S) and had a significantly longer overall survival compared to CRT (p<0.0001), with median survival of 40.6mo (95% CI 32.3, 55.5) in the CRT+S group and 17.3mo (95% CI 13.3, 36.4) in the CRT group. Among 74 high-risk patients, 41 (55.4%) were treated with surgery. We did not find a difference in overall survival between the surgical group (CRT+S) and the group treated with CRT alone (p=0.34). The median survival was 27.4mo (95% CI 15.8, 32.9) in the CRT group compared to 23.0mo (95% CI 14.7, 54.4) in the CRT+S group.

**Conclusions:** Our retrospective study demonstrates that for low-risk patients with adenocarcinoma of the esophagus, there is a survival benefit to the addition of surgery. Conversely, we failed to detect a survival benefit to the addition of surgery in the highest-risk quartile of patients. Measurement of body composition may help identify a high-risk subset of patients with locally advanced adenocarcinoma of the esophagus who may benefit from forgoing surgery after chemoradiation. Research Sponsor: None.
Moving towards a personalised understanding of the nutritional impact of self-expanding metallic stents (SEMS) in gastro-oesophageal cancer: A retrospective case note review of a tertiary referral oncology centre. First Author: Aimee Cunningham, The Christie NHS Foundation Trust, Manchester, United Kingdom

Background: Dysphagia is a common life-impacting complication for patients with gastro-oesophageal (G-O) cancer. Options to alleviate dysphagia include insertion of SEMS or percutaneous endoscopic gastrostomy (PEG). SEMS improve quality of life by enabling a person to eat a varied diet, but are associated with complications including pain and need for reintervention. Although studies have shown SEMS improve dysphagia, consequent longitudinal impact on nutritional status has not been evaluated. There is a need to better characterise risks and benefits of SEMS to allow a personalised approach to both insertion and follow-up. Methods: We identified patients with a confirmed diagnosis of O-G cancer, who underwent SEMS insertion at The Christie NHS Foundation Trust in 2021 and 2022. Data was retrospectively collected about patient and stent characteristics, and patient outcomes to quantify benefits and risks of SEMS. Results: 112 patients had 127 SEMS inserted at The Christie. Patients’ International Dysphagia Diet Standardisation Initiative (IDDSI) score significantly improved after SEMS insertion (N=120); prior to SEMS 62% were only managing liquids and purees (IDDSI 3 and 4) and 24% were not able to eat enterally. Post SEMS, 76% tolerated textured foods (IDDSI 5 and above) and only 21.5% were limited to liquids/purees. We observed a significant reduction in the rate of weight loss (% body weight/10 days) following SEMS insertion (-0.010 ± 0.009 vs. -0.01 ± 0.010, P < 0.001). 12% of patients experienced grade 3 SEMS-related toxicity or stent failure within 30 days, and 20% developed significance pain within 24 hours of SEMS insertion. Conclusions: SEMS provide meaningful nutritional benefit in the majority of patients with O-G cancer, as weight loss is significantly slowed following insertion. However, we identified two groups of patients who did not benefit from SEMS; those who continued to lose weight and those who had stent failure. We did not find predictive factors for stent failure from multivariate analysis baseline demographics or stent characteristics. Therefore, more detailed analysis of tumour factors, imaging findings and SEMS location from a larger cohort of patients may be required to identify patients who are unlikely to benefit from SEMS, and alternative interventions such as PEG feeding could be considered. Research Sponsor: None.

Efficacy and safety of nivolumab and CapeOX in patients with previously untreated FGFR2-positive, PD-L1-positive advanced gastric cancer: A single-arm, multicenter, phase 2 study NIVOFGFR2. First Author: Ilya Tsimafeyeu, Bureau for Cancer Research - BUCARE, New York, NY

Background: Nivolumab in combination with chemotherapy has been approved in the first line treatment of PD-L1 positive, PD-L1/low or PD-L1 negative metastatic GC (GC). Fibroblast growth factor receptor 2 (FGFR2) is overexpressed in 30% of patients with GC and is a potential new target for targeted therapy with monoclonal antibodies or allospecific extracellular inhibitors. The aim of the NIVOFGFR2 study was to evaluate the preliminary efficacy of nivolumab in metastatic GC co-expressing PD-L1 and FGFR2. Methods: In this single-center, phase 2, open-label study, we enrolled metastatic GC with PD-L1 expression >1% and HER2-negative gastric adenocarcinoma with centrally confirmed expression of PD-L1 (CD274) >1% and/or FGFR2 (moderate, grade 2) and FGFR2 (strong, grade 3) membranous staining in more than 1% of tumor cells; Ab $p$ = 0.05 and the power of 90%. Results: Thirty patients from 14 institutions were enrolled between March 2021 and June 2022. Data was retrospectively collected about patient and taste was examined for each AE. Results: A total of 18 patients (9 with esophageal cancer, 8 with colorectal cancer, and 1 with gastric cancer) were enrolled in this study. Palliative chemotherapy was given to 9 patients and preoperative chemotherapy to 9. AEs (any grade) related to chemotherapy-induced eating disorders were anorexia in 13 patients, dysgeusia in 12, nausea in 10, and oral mucositis in 7. Median food intake and taste scores for all patients were 95.7%, sweet 50.3, salty 50.1, sour 49.5, bitter 48.4, umami 53.2, and spicy 45.6. When assessed by CTCAEs, the following were found: anorexia 100%, dysgeusia 95.7%, sweet 48.3, salty 53.1, sour 48.0, bitter 46.2, umami 53.2, spicy 45.6; nausea 92.0%, sweet 50.1, salty 50.6, sour 49.4, bitter 45.8, umami 50.3, spicy 46.4; and oral mucositis 94.1%, sweet 47.6, salty 50.4, sour 47.0, bitter 48.9, umami 52.0, spicy 47.0. Compared with all patients, in anorexia there were no obvious sensitivities for any foods, but in the intake amount was decreased. In dysgeusia, patients less strongly perceived sweet and spicy, but more strongly perceived salty and umami. In nausea, the patients ate less and less strongly perceived bitter, umami, and spicy. In oral mucositis, sweet and sour tastes were perceived less strongly. Conclusions: By using a dietary app, detailed taste could be quantified for chemotherapy AEs related to eating disorders. Further large-scale studies may be needed. Clinical trial information: UMIN000028749. Research Sponsor: None.

A phase II study of perioperative cepatibacine plus oxaplatin (CapeOx) therapy for advanced gastric cancer with multiple lymph node metastases (OGSS 1701). First Author: Shunji Endo, Kawasaki Medical School, Kurashiki, Japan

Background: Gastric cancer with paraaortic lymph node metastasis or bulky lymph node metastasis is difficult to undergo curative resection without preoperative chemotherapy (GC). Perioperative chemotherapy may improve cure rates in patients with metastatic gastric adenocarcinoma (GC). The aim of the NIVOFGFR2 study was to evaluate the preliminary efficacy and safety of perioperative cepatibacine plus oxaplatin combined chemotherapy (CapeOx) for such advanced gastric cancer with multiple lymph node metastases. Methods: In this phase II trial, eligibility criteria were as follows; histologically proven gastric carcinoma, HER2-negative or unknown, and no prior chemotherapy or radiotherapy (URR) for URR > 3.0 cm and/or bulky lymph node metastases located at celiac axis, common hepatic, splenic artery and/or upper mesenteric vein which make a huge bulk > 3.0 cm and/or multiple large bulks > 1.5 cm; without any other metastatic lesions; not a large (> 8 cm) type 3 or type 4 gastric cancer; and age between 20 and 80 years old. Treatment included three cycles of perioperative CapeOx (cepatibacine: 2,000 mg/m² for 14 days; oxaplatin: 130 mg/m² day 1) every 3 weeks, followed by five cycles of postoperative CapeOx after radical gastrectomy. The primary endpoint was response rate according to the RECIST v1.0. The planned sample size was 30 patients calculated on the hypothesis that the expected response rate was 65% and the threshold was 50%, with one-sided alpha of 0.05 and the power of 90%. Results: Thirty patients from 14 institutions were enrolled from September 2017 to June 2022. The number of patients who had complete response, partial response, stable disease, progressive disease, and inevaluable were, 0, 20, 8, 1, and 1, respectively. The response rate was 66.7%, with the 90% confidence interval of 50.1 - 80.7% (p = 0.049). The curative resection rate was 93.3%. The protocol treatment completion rate was 93.3%. The perioperative chemotheraphy completion rate was 90.0%. The operation completion rate was 90.0%. The postoperative chemotherapy completion rate was 70.0%. The relative dose intensities were 94.8% for cepatibacine and 95.2% for oxaplatin on perioperative CapeOx, and 80.8% for cepatibacine and 64.2% for oxaplatin on postoperative CapeOx. The histological response rate (Grade ≥ 1b) was 66.7%. The adverse events of Grade ≥ 3 included neutropenia in 3.3%, anemia in 10% on perioperative CapeOx, and neutropenia in 23.8% and diarrhea in 9.5% on postoperative CapeOx. The final results of the survival analysis are yet to come. Conclusions: Perioperative CapeOx therapy for advanced gastric cancer with multiple lymph node metastasis showed favorable response rate, curative resection rate and acceptable adverse events, and was considered a promising treatment regimen. Clinical trial information: UMIN000028749. Research Sponsor: None.
Pathologic complete response among patients with esophageal cancer receiving neoadjuvant chemotherapy or chemoradiation: A meta-analysis.

First Author: Charles Gaber, University of Illinois-Chicago, Chicago, Illinois, United States

Background: Although neoadjuvant therapy improves overall survival in esophageal cancers, the benefit is largely confined to those with the greatest pathologic response. Current estimates of pathologic complete response (pCR) rates come from individual studies and lack precision. With this study, we sought to estimate summary pCR rates in patients with non-metastatic esophageal cancer who received either neoadjuvant chemotherapy or chemoradiation by conducting a systematic review and meta-analysis of clinical trials.

Methods: Studies were identified from the Medline, EMBASE, and CENTRAL database searches. Eligible studies were published in English from 1992-2022 and consisted of clinical trials that focused on incident non-metastatic esophageal cancer or cancer of the gastroesophageal junction. Trials were required to contain at least one arm of patients receiving neoadjuvant chemotherapy (including perioperative) or neoadjuvant chemoradiation (including treatment with induction chemotherapy). Eligible studies had to report pCR in at least 20 patients who underwent neoadjuvant therapy and surgery. Pooled pCR prevalence was determined using the Freeman-Tukey double arc sine transformation and a random effects model. Results: Among 6,575 records identified, we included 75 studies with 5,988 patients in the meta-analysis. Of the included studies, 38 (51%) were single arm trials, 35 (47%) were randomized trials, and 2 (3%) were non-randomized trials of multiple treatments. Geographically, 28 (37%), 24 (32%), 21 (28%), and 2 (3%) of the included trials were performed in Asia, Europe, North America, and Australia, respectively. Across 91 trial arms that delivered either neoadjuvant chemotherapy or chemoradiation, platinum and fluorouracil-based regimens were the most common (48.4%), followed by platinum and taxane-based regimens (26.4%), regimens that contained platinum-based agents, fluorouracil, and a taxane (13.2%), and other regimens (12.1%). The pooled prevalence of pCR after neoadjuvant chemotherapy in squamous cell carcinomas was 9% (95% CI: 6% - 14%) across 16 studies, ranging from 0%-32%. The pooled prevalence of pCR after neoadjuvant chemoradiation was 32% (95% CI: 26% - 39%) across 21 studies, ranging from 8% to 66%. For adenocarcinomas, the pooled prevalence of pCR was 2% (95% CI: 0% - 7%) after neoadjuvant chemotherapy, across 3 studies, and 22% (17% - 27%) after neoadjuvant chemoradiation across 11 studies. Conclusions: In this meta-analysis, we evaluated outcomes for patients with non-metastatic esophageal cancer who receive neoadjuvant chemo(radiation) experience pCR. As pCR represents an increasingly utilized as an endpoint in neoadjuvant trials, these estimates of pooled pCR rates may serve as an important benchmark for future trial design. Research Sponsor: None.

Clinical outcomes of primary esophagectomy and secondary esophagectomy after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma: A propensity-score matched analysis.

First Author: Minjee Kim, Samsung Medical Center, Seoul, South Korea

Background: Currently it is unknown whether secondary esophagectomy after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma was 32% (95% CI: 26% - 39%) across 21 studies, ranging from 8% to 66%. For adenocarcinomas, the pooled prevalence of pCR was 2% (95% CI: 0% - 7%) after neoadjuvant chemotherapy, across 3 studies, and 22% (17% - 27%) after neoadjuvant chemoradiation across 11 studies. Conclusions: In this meta-analysis, we evaluated outcomes for patients with non-metastatic esophageal cancer who receive neoadjuvant chemo(radiation) experience pCR. As pCR represents an increasingly utilized as an endpoint in neoadjuvant trials, these estimates of pooled pCR rates may serve as an important benchmark for future trial design. Research Sponsor: None.

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Phase 2 study of trastuzumab deruxtecan as neoadjuvant treatment for HER2-positive gastric and gastroesophageal junction adenocarcinoma (EPOC2003).

First Author: Daisuke Takahari, Gastroenterological Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto City, Tokyo, Japan

Background: Currently no HER2 directed therapy is available in the perioperative setting for gastric and gastroesophageal junction (GEJ) cancer. Trastuzumab deruxtecan (T-DXd) received regulatory approval based on the encouraging efficacy demonstrated in the DESTINY-Gastric01 and DESTINY-Gastric02 studies in pretreated patients (pts) with metastatic gastric and GEJ cancer. This multicenter phase 2 study aimed to evaluate the clinical activity and safety of neoadjuvant T-DXd for locally advanced gastric and GEJ cancer.

Methods: Eligible pts possessed previously untreated locally advanced gastric and GEJ adenocarcinoma with clinical stage of T2-4 and/or N+ without distant metastasis. The main cohort enrolled pts exhibiting HER2-positive, defined as IHC 3+ or IHC 2+ with ISH by local assessment. An exploratory cohort included pts with HER2-low expression (IHC 1+ or 2+ with negative) with serum HER2 ECD exceeded 11.6 ng/mL. Treatment included three cycles of T-DXd administered every 3 weeks, followed by surgery. The primary endpoint was the major pathological response (MPR) rate by central assessment, with an expected rate of 45% and a futility threshold of 20%. The planned sample size in the main cohort was 27 pts with one-sided alpha of 10% and power of 90%, while an additional 10 pts would be enrolled into the exploratory cohort.

Pre- and post-treatment samples were subjected to biomarker analyses. Clinical trial identification: NCT05034887. Results: Between November 2021 and November 2022, 27 pts were enrolled into the main cohort from seven Japanese sites. The majority of the pts had IHC2+ (24pts). The primary sites were gastric (16 pts) and GEJ (11 pts). Clinical stage ranged from IIIA/IIIB/IIIC. 4 pts observed 3 courses of T-DXd and one pt discontinued because of toxicity. R0 resection was achieved in 25 pts, with one undergoing R1 resection. The MPR rate as the primary endpoint was 14.8% (80CI 6.6% - 27.5%) which did not surpass the predefined 20%. The pCR rate was 3.7% (95CI 0.1% - 19.0%). There were no new safety signals during T-DXd treatment and during the post-surgery phase. Biomarker analyses remain ongoing.

Conclusions: T-DXd monotherapy showed modest single agent activity for locally advanced HER2-positive gastric or GEJ adenocarcinoma in this phase 2 study. An additional cohort combining perioperative T-DXd with capecitabine and durvalumab is planned, to assess whether treatment efficacy and outcomes can be enhanced. Clinical trial information: NCT05034887. Research Sponsor: Daiichi-Sankyo.

Larynx-preserving treatment strategy for patients with resectable cervical esophageal squamous cell carcinoma.

First Author: Yasuhiro Tsushima, Division of Esophageal Surgery, Shizuoka Cancer Center, Shizuoka, Japan

Background: Preservation of the larynx is an important treatment strategy for cervical esophageal squamous cell carcinoma (CESCC), because surgery for CESCC often involves radical resection of the neck. Therefore, dCRT (corticosteroids, 5-fluorouracil + radiation G0y) to preserve laryngeal function. In this study, we compared the treatment results of esophagectomy and definitive chemoradiotherapy (dCRT) for resectable CESCC and examined larynx-preserving treatment strategies.

Methods: Patients who were treated for resectable CESCC at our hospital from January 2003 to March 2021 were divided into the surgery group and the CRT group, and their outcomes were compared. The primary endpoint was R0 resection rate. All patients were eligible for both treatments. The treatment results were compared retrospectively.

Results: Of all 61 patients, 23 patients received surgery and 38 received CRT. There was no significant difference in patients’ characteristics between the two groups. In surgery group, 19 cases lost their laryngeal function by surgery (82.6%). Recurrence was observed in 7 cases, of which only 3 cases was local. In CRT group, 33 cases (86.8%) achieved complete response, of which 16 cases relapsed, 8 cases (21.1%) lost their laryngeal function by additional surgery after CRT. There was no significant difference in recurrence between two groups (surgery, 60.8%; CRT, 70.1%; p = 0.735). In CRT group, 5-year larynx-preserving survival rate was 64.8%, and esophageal stenosis before treatment was the independent risk factor for non-larynx preservation. 5-year larynx-preserving survival rate was 78.5%, and 5-year survival rate was 85.4% for non-stenotic cases in treatment group, which were significantly higher than those for stenotic cases. 5-year larynx-preserving survival rate was also high in the patients with Ce localized tumor (72.6%). In those patients, non-stenotic patients and CT1-T3 patients had significantly high 5-year larynx-preserving survival rate (87.5% and 92.3%).

Conclusions: dCRT for CESCC was comparable to surgery in terms of long-term prognosis, and the rate of larynx preservation was high. Among the cases where the tumor was localized to Ce, the laryngeal preservation rate was particularly high in non-stenotic cases and cases with CT1-T3, and dCRT should be actively indicated for these cases. Research Sponsor: None.

The efficacy and safety of conversion therapy after initial systemic chemotherapy in advanced esophageal cancer with distant metastases: A multi-center retrospective observational study.

First Author: Takehiro Ito, Department of Surgery, Keio University School of Medicine, Shingu Ku-Ku, Kanagawa, Japan

Background: Systemic chemotherapy, with or without radiation, has been the standard treatment for esophageal squamous cell carcinoma (ESCC) with distant metastasis. The increased efficacy of multimodality treatment allows for the consideration of conversion therapy with curative intent for initially unresectable ESCC after initial treatment. In the present study, we examined the safety and effectiveness of conversion therapy for ESCC between 2011 and 2021 at participating institutions retrospectively reviewed.

Methods: From 22 institutions, 140 patients were enrolled. As all the patients received systemic chemotherapy as an initial treatment. The distant metastatic sites in para-aortic lymph nodes/extra regional mediastinal lymph nodes/lung/liver/bronchus/other were 81(54%)/19(13%)/14(9%)/11(7%)/4(3%)/29(14%), respectively. After the initial treatment, 116 patients underwent surgery and 33 patients received CRT as conversion therapy. Of 116 patients who underwent conversion surgery, the incidence of postoperative pneumonia/leakage/recurrent laryngeal nerve palsy was 16%/7%/6%, respectively. R0 resection was obtained in 87%. Regarding the non-hematological toxicities during conversion CRT (CTCAE grade 3 or higher), decreased appetite/dysphagia/esophagitis was 21%/15%/9%, respectively. No grade 4 or higher hematologic toxicities were observed. The 5-year OS (3y-OS) rate for all patients was 41.9%, and no significant differences were found between surgery and CRT groups (43.3% vs 37.0%, p = 0.112). Pathological responders showed a significantly longer OS than non-responders (3y-OS, 56.4% vs 36.1%, p = 0.010). The distribution or number of distant metastases were not identified as prognostic factors.

Conclusions: This study showed that conversion therapy for ESCC patients with distant metastasis could be considered safe and have a favorable prognosis. Since its survival benefit would depend on the pathological response before surgery and carefully select appropriate candidates of conversion therapy in ESCC. Research Sponsor: None.

Atezolizumab and trastuzumab plus chemotherapy in patients with HER2+ locally advanced resectable gastric cancer or adenocarcinoma of the gas- troesophageal junction: A multi-center, randomized, open-label phase II study.

First Author: Zhi Peng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Surgery, Institute of Cancer Prevention and Treatment, Peking University Cancer Hospital and Institute, Haidian District, Beijing, Beijing, China

Background: Currently, there are no standard perioperative regimens for human epidermal growth factor receptor 2 positive (HER2+) gastric (GC) or gastroesophageal junction (GEJ) cancer. Furthermore, despite advances in neoadjuvant or perioperative chemotherapy, the efficacy of treatment for locally resectable advanced GC or GEJ cancer remains un- satisfactory. Method: Patients aged 18–75 years were randomized 1:1 to receive atezolizumab + trastuzumab (Arm A) or trastuzumab + XELOX (Arm B) and received the regimen for three neoadjuvant cycles (3 weeks per cycle) and five adjuvant cycles. Treatment administration was atezolizumab 1200 mg, trastuzumab 6 mg/kg, oxaliplatin 130 mg/m² intravenously on Day 1, and capecitabine 1000 mg/m² orally twice daily on Days 1–14 of each 3-week cycle. The primary endpoint was the pathological complete regression (pCR) rate. Secondary endpoints were the objective response rate (ORR) during neoadjuvant systemic therapy (NAST) and the R0 resection rate. Time-to-event endpoints are not reported because of immaturity. Efficacy endpoints were analyzed in the intention-to-treat (ITT) population and the primary analysis was with 12 March 2023.

Results: Forty-two Asian patients who participated in the trial (Arm A = 21 and Arm B = 21), all patients completed NAST. Most patients were male (92.9%), and the median (range) age was 61 (33–72) years in Arm A and 65 (46–72) years in Arm B. The pCR rate was 38.1% (8/21) in Arm A and 14.3% (3/21) in Arm B (treatment difference: 23.8% [90% confidence interval (CI), 1.3%–44.7%]). The pCR rate was significantly better in Arm A than in Arm B (P = 0.079 < 0.1; lower limit of the 90% CI > 0). Subgroup analysis showed that age < 65 years, male sex, and intestinal Lauren classi- fication were associated with a better pCR rate for the atezolizumab inclusive treatment arm (Arm A); however, these results require further confirmation in future studies. No significant difference was detected between the two arms in ORR during NAST or the R0 resection rate.

Conclusions: The addition of atezolizumab to trastuzumab + XELOX therapy was effective in patients with HER2+ locally advanced resectable GC or adenocarcinoma of the GEJ. Clinical trial information: NCT04601152. Research Sponsor: F. Hoffmann-La Roche Ltd.
Neutrophil-to-lymphocyte ratio to predict metastachronous cancer after curative resection of early gastric cancer. First Author: Sunsook Kim, Korea University Guro Hospital Care System, Seoul, South Korea

Background: We investigate the predictive value of inflammatory markers for occurrence of metachronous cancers among patients who underwent endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) and are judged as curative resection (CR).

Methods: We enrolled patients who were diagnosed as EGC and underwent ESD during 2006 and 2020. We retrospectively collected data of inflammatory indexes such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and erythrocyte sediment ratio (ESR). Results: A total of 1,011 patients underwent ESD for EGC, achieved CR and were followed up more than 12 months. Among these, 86 patients had metachronous cancers (85/1011, 8.4%) during 53.4 months of follow-up. Compared with patients without metachronous cancers, those with metachronous cancers were significantly older (65.9 vs 63.8 years, P = 0.004) and had higher NLR (2.1 vs 1.8, P = 0.002). However, other inflammatory indexes such as PLR and ESR were not significantly different between two groups.

Kaplan-Meier analysis showed that patients with NLR \( \geq 2.0 \) had significantly higher possibility of metachronous cancer compared with patients with NLR < 2.0 (P = 0.049 by log rank test). After adjusting for age, atrophy and Helicobacter pylori status, NLR was the only significant risk factor for metachronous metastasis (odds ratio: 1.33, 95% confidence interval: 1.007-1.665, P = 0.011).

Conclusions: NLR may have a predictive value for occurrence of metachronous cancer after CR of EGC by ESD. Further thorough investigation is necessary to validate this outcome. Research Sponsor: None.

Clinical outcomes of early gastric cancer resected by endoscopic submucosal dissection at young age. First Author: Jong-Jae Park, Korea University Guro Hospital, Korea University College of Medicine, Seoul, South Korea

Background: A small portion of patients are diagnosed as early gastric cancer (EGC) and undergo endoscopic submucosal dissection (ESD) at young age. However, their clinical outcomes are rarely known. We investigated clinical characteristics and outcomes of patients who underwent ESD for treatment of EGC at age under 50.

Methods: We enrolled patients who were diagnosed as EGC and underwent ESD during 2006 and 2020. We divided them either for young age (YA) group if age < 50 years and other age (OA) group if > 50 years. Results: We enrolled 1,349 patients (YA group: 105 patients [7.8%], OA group: 1,244 [92.2%]). Compared with OA group, YA group contained more female patients (36.2 vs. 26.5%, P = 0.033), their tumor was located at middle third (41.0 vs. 29.6%, P = 0.006) and was depressed (40.0 vs. 28.8%, P = 0.001), and had more undifferentiated (30.5 vs. 12.1%, P < 0.001) and diffusetype (22.9 vs. 7.3%, P < 0.001) histology. However, synchronous tumor was less frequent in YA group (2.9 vs. 12.4%, P = 0.001). When we sorted 884 patients who achieved curative resection and were followedup longer than 12 months, Kaplan-Meier analysis showed that metastachronous neoplasm (dysplasia or cancer) and metachronous cancer were significantly less in YA group than OA group (P = 0.003 and 0.013, respectively), however, local recurrence was not significantly different between two groups.

Conclusions: ESD is a favorable and effective therapeutic modality for EGC patients who are aged under 50, once curative resection is achieved. Research Sponsor: None.
A phase I/II study of ASKB589 (anti-Claudin 18.2 [CLDN18.2] monoclonal antibody) combined with CAPOX and PD-1 inhibitor as first-line treatment for locally advanced, relapsed and metastatic gastric/oesophageal junction (G/GEJ) adenocarcinoma. First Author: Zhi Peng, Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China. Background: ASKB589 is a humanized IgG1 monoclonal antibody against Claudin 18.2 (CLDN18.2) with high affinity and enhanced antibody-dependent cytotoxicity. We report preliminary safety and efficacy data from an ongoing Phase I/II, dose-escalation and expansion study of ASKB589 combined with cetaplatin, oxaplatin(CAPOX) and Sintilimab as first-line treatment of G/GEJ adenocarcinoma (NCT05632939). Methods: The study enrolled G/GEJ adenocarcinoma patients(pts) with CLDN18.2 positive expression. The dose-escalation phase used a 3 + 3 design to determine the maximum tolerated dose (MTD). In expansion, pts received ASKB589 intravenously (IV) at doses of 6 mg/kg (n = 3) and 10 mg/kg (n = 6) every 3 weeks (Q3W) combined with CAPOX and Sintilimab. In expansion, all pts received ASKB589 IV at a dose of 6 mg/kg. Results: As of July 20, 2023, 9 pts were enrolled in escalation. No DLT was observed and thus the MTD was not identified. 9(100) pts had treatment-related adverse events (TRAEs), the most common being nausea (77.7%), hypoproteinemia (66.7%), and anemia (55.6%). While the majority of TRAEs were grade 1 or 2, 1 pt (11.1%) had a grade 3 TRAE (decreased neutrophils [10mg/kg]). In expansion, 26 pts with CLDN18.2 moderate-to-high expression (≥2+) expressed the staining intensity in ≥40% of tumor cells were included in the safety set. 24(92.3%) pts had at least one post-baseline tumor assessment. 12 pts (80.0%) achieved PR for an unconfirmed objective response rate (ORR) of 80.0%. 3 pts (20.0%) had SD for a disease control rate (DCR) of 100.0%. The PK of ASKB589 at doses of 6mg/kg and 10mg/kg combined with CAPOX and anti-PD1 therapy was consistent with that of monotherapy. Conclusions: ASKB589 combined with CAPOX and anti-PD1 therapy was well tolerated in pts with gastroesophageal (GE) cancer with liver metastasis. Clinical trial information: NCT05632939. Research Sponsor: None.

Poster Session

First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) vs chemo in patients (pts) with advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (G/GEJ/OC). CheckMate 649 Chinese subgroup analysis 4-year (yr) follow-up. First Author: Lin Shen, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China. Background: NIVO + chemo demonstrated clinically meaningful improvement in overall survival (OS) and an acceptable safety profile vs chemo in previously untreated Chinese pts from CheckMate 649; consistent with the overall study population with advanced G/GEJ/OC. 1L NIVO + chemo is approved for advanced G/GEJ/OC in multiple countries, including China. We report 4-yr results of NIVO + chemo vs chemo in Chinese pts from CheckMate 649. Methods: Adults with previously untreated, unresectable advanced or metastatic, non-HER2+ G/GEJ/OC were enrolled regardless of programmed death ligand 1 (PD-L1) expression. Randomized pts received NIVO (360 mg q3w) + chemo (CELOX or FOLFIRINOX), NIVO + pembrolizumab, or chemo. Dual primary endpoints for NIVO + chemo vs chemo were OS and progression-free survival (PFS) by blind independent central review (BICR) in pts with PD-L1 combined positive score (CPS) ≥ 5. Results: 208 Chinese randomized to NIVO + chemo or chemo. At 49-month (mo) minimum follow-up, NIVO + chemo continued to demonstrate OS and PFS benefit vs chemo in pts with PD-L1 CPS ≥ 5 and in all randomized pts (Table). The 4-yr OS rate was 25% with NIVO + chemo vs 11% with chemo in pts with PD-L1 CPS ≥ 5 and 21% vs 9% in all randomized pts. Objective response rate (ORR) (95% CI) 15.4% (9.9–21.5) vs 7.4% (4.1–11.7) in the all randomized pts (ORR [95% CI] 12.5 mo [7.2–21.7] vs 6.9 mo [3.8–9.4]) and in all randomized pts (mPFS [95% CI] 12.5 mo [7.2–17.7] vs 5.6 mo [4.8–6.6]). No new safety signals were identified (Table). Conclusions: After 4 yrs of follow-up, NIVO + chemo continued to demonstrate clinically meaningful survival benefit and more durable OS vs chemo in Chinese pts, with an acceptable safety profile. These results are consistent with previous reports and with the overall study population with advanced G/GEJ/OC and further support NIVO + chemo as a standard 1L treatment option for Chinese pts. Clinical trial information: NCT02975116. Research Sponsor: Bristol Myers Squibb.

Role of immunotherapy in gastroesophageal cancer with liver metastasis: A meta-analysis of phase III randomized clinical trials. First Author: Sawyer Bawek, Department of Internal Medicine, University at Buffalo, Buffalo, NY. Background: Recent studies have demonstrated a poor response to immunotherapy in patients with colorectal cancer with liver metastasis. The role of immune checkpoint inhibitors (ICIs) as first-line treatment in gastroesophageal (GE) cancers remains unclear. Our objective was to investigate if ICIs are beneficial in patients with GE cancer with liver metastasis. Methods: We searched PubMed, Embase, ESMO, and ASCO Meeting Abstracts for phase III randomized clinical trials (RCTs) testing ICIs in metastatic/advanced GE cancer from 2017 to 2023. All phase III RCTs of metastatic GE cancer with available data on liver metastases were included in the meta-analysis. Results were conducted on the survival outcomes (overall and progression-free survival), where hazard ratios were obtained, with 95% confidence intervals, using the standard random effects model. To assess the heterogeneity of the study outcomes, the I2 statistic was obtained. The I2 statistic represented the variability in the meta-analysis attributed to study heterogeneity. These analyses were applied to the overall cohort of studies, as well as within the liver metastasis (yes or no) sub-cohorts. All analyses were conducted in SAS v9.4 (Cary, NC) at a significance level of 0.05. Results: Seven Phase III RCTs were included that had available data on overall survival and/or progressive free survival in patients with liver metastasis. Of these, six were in the frontline setting and one in the later line. Overall, 6,109 patients were included. Overall survival was similar among all patients (HR 0.72 [0.67-0.77], p < 0.001, I2%0), patients with no liver metastasis (HR 0.73 [0.67,0.81], p < 0.001, I2=0%), patients with liver metastasis (HR 0.74 [0.67,0.81], p < 0.001, I2=0%), indicating that ICIs benefit on OS is consistent. Progression-free survival (PFS) was also similar among all patients (HR 0.63 [0.57,0.70], p < 0.001, I2=54.7%), with no liver metastasis (HR 0.62 [0.51,0.76], p < 0.001, I2=62.3%), and with liver metastasis (HR 0.66 [0.57,0.76], p < 0.001, I2=0%). Funnel plots were used to identify a potential bias for studies included in the analysis and showed no significant sources of bias for OS and PFS. Conclusions: In this meta-analysis, ICIs were beneficial in patients with GE cancer with and without liver metastasis, and the majority of the trials were conducted on advanced gastric cancer with liver metastasis combined with chemotherapy. Further subgroup analyses should be performed with individual patient-level data to identify patients who respond best to ICIs. Research Sponsor: None.

Efficacy

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<th>NIVO + chemo (n = 150)</th>
<th>Chemo (n = 150)</th>
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<tr>
<td>OS (1L)</td>
<td>11.5 (9.3–13.7)</td>
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<td>PFS (1L)</td>
<td>5.6 (4.4–6.9)</td>
<td>5.2 (4.0–6.3)</td>
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<td>OS (All RCTs)</td>
<td>11.9 (10.6–13.2)</td>
<td>9.3 (8.1–9.6)</td>
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<tr>
<td>PFS (All RCTs)</td>
<td>5.4 (4.2–6.6)</td>
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**Safety, all treated pts:** TRAEs, n (%)

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<th></th>
<th>NIVO + chemo (n = 99)</th>
<th>Chemo (n = 106)</th>
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<tr>
<td>Any grade</td>
<td>95/96 (96/96)</td>
<td>100/96 (96/96)</td>
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<tr>
<td>≥3 TRAEs</td>
<td>76/95 (76/76)</td>
<td>75/94 (71/72)</td>
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**TRAEs**

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Clinicopathological characteristics and lymph node metastasis rates in early gastric lymphoepithelioma-like carcinoma: Implications for endoscopic resection.

First Author: Tae-Se Kim, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: To clarify the clinicopathological features and the rate of lymph node metastases (LNM) of early gastric lymphoepithelioma-like carcinoma (LELC).

Methods: We compared the clinicopathological characteristics of 82 LELC and 5758 well- or moderately differentiated (WD or MD) tubular adenocarcinoma patients who received gastrectomy for single early gastric cancer (EGC).

Results: Compared to the control group, early LELC patients were younger, had a higher prevalence of proximally located tumors, more frequent Epstein-Barr virus (EBV) infection, more frequent deep submucosal invasion (SM2 or SM3, 85.4% versus 29.9%, P < 0.001) but less frequent lymphatic invasion (4.9% versus 16.2%, P = 0.009). Among tumors with deep submucosal invasion, early LELC patients had smaller tumors, less frequent lymphatic invasion (6.7% versus 40.1%, P < 0.001) and a lower rate of LNM (7.1% versus 19.4%, P = 0.016) than the control group. LNM rates of LELC patients with mucosal, shallow submucosal invasion (SM1) and deep submucosal invasion were 0%, 0%, and 7.1%, respectively. Lymphatic invasion was the only significant risk factor in the regression analysis for LNM in LELC patients. Among 12 patients with mucosal or shallow submucosal invasion and 27 patients with deep submucosal invasion having small tumor sizes (less than 2 cm) and no lymphatic invasion, there was no LNM.

Conclusions: Given the low rate of LNM, the same curability criteria of ESD for WD or MD EGC may be applied to early LELC and even more flexibly for those considered non-curative ESD only because of deep submucosal invasion. Research Sponsor: None.

A phase 2 study of fruquintinib in combination with S-1 for second-line treatment of esophageal squamous cell carcinoma after first-line immunotherapy failure.

First Author: Ningli Li, Peking Union Medical College Hospital, Beijing, China

Background: Patients with advanced esophageal squamous carcinoma (ESCC) who experience progression after first-line immunotherapy face a challenging treatment landscape. The potential of anti-vascular therapy combined with chemotherapy in the treatment of esophageal cancer is well-established. Mechanistically, anti-angiogenic agents can promote the normalization of tumor vasculature and facilitate the access of chemotherapy agents to tumor targets. Considering the compromised physical condition of advanced ESCC patients, there is a preference for more convenient oral medications. Therefore, we conducted this phase II study to assess the clinical efficacy and safety of combining fruquintinib with 5-FU plus S-1 in treating advanced ESCC patients following first-line immunotherapy failure.

Methods: This open-label, single-arm, phase II study consists of dose-finding and dose-expansion phases, enrolling 30 advanced or metastatic ESCC patients after first-line immunotherapy failure. The dose-finding phase followed a 3+3 design. Patients received fruquintinib (3mg, 4mg, 5mg, d1-d14, q3w, respectively), in combination with S-1 (40mg, 50mg, 60mg, bid, d1-d14, q3w, based on body surface area (BSA)), until progression, unacceptable toxicity, progressive disease, or death. The initial fruquintinib dose was 4mg d1-d14, q3w, in combination with an appropriate S-1 dose. Additional patients were enrolled in the dose-expansion phase and received the maximum tolerated dose determined in the dose-finding phase.

Results: A total of 240 patients were randomized to bDCF (n=121) and CT (n=119) between September 2014 to April 2021. Patient background in bDCF/CF arm was median age, 65/64 years; ECOG performance status 0/0%, 75%; metastatic disease, 63%/67%, >2 metastatic organs, 59%/56%; squamous cell carcinoma, 94%/97%. As a data cut-off of April 2023, all 240 patients discontinued protocol treatment. The reasons for treatment discontinuation in bDCF arm were disease progression, 58%/71%; adverse events (AEs), 35%/27%; refusal, 15%/1%; others, 7%/5%, respectively. With a median follow-up of 15.2 months (m), bDCF arm was not superior to CF arm in terms of OS with a median of 16.2 m [HR, 0.75 (0.44, 1.26)] and 25.8%/45.6%/ Major grade 3 or 4 AEs observed in bDCF/CF arm were neutropenia (37.8%/27.1%), anemia (25.2%/16.1%), fatigue (10.1%/13.5%), hypotension (13.4%/13.6%). No treatment related death was observed. Subsequent therapy in bDCF/CF arm was provided for 87%/89% of patients. Conclusions: JCOG1314 did not reach its primary endpoint; although bDCF combination associated with S-1 showed the promising clinical benefit and is still the standard therapy in patients with metastatic or recurrent esophageal cancer if ICIs are not applicable. Clinical trial information: jRCTs031180143. Research Sponsor: AMED.
325 Poster Session

Network meta-analysis of global trials of 1L therapies in locally advanced (LA) resectable or metastatic gastric or gastroesophageal junction (mGEJ) adenocarcinoma. First Author: Mansh A. Shah, Weill Cornell Medical College, New York, NY.

Background: The phase 3 SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) studies reported statistically significant improvement in PFS and OS with 1L nivolumab (anti-CTLA4) or pembrolizumab (anti-PD-L1). This network meta-analysis (NMA) indirectly compared the relative efficacy of 1L therapies. Methods: A systematic literature review of phase 2, 3, or unknown phase randomized, global trials of 1L therapies (cetuximab + cisplatin [CX]; cetuximab + oxaliplatin [CAPOX]; cetuximab + folinic acid + fluorouracil [FOLFOX]; 5-FU + cisplatin [F-P]) with pembrolizumab + FOLFOX, pembrolizumab + CX, and zolbetuximab + CAPOX/FOX/CAPOX in adults with LA unresectable or mGEJ adenocarcinoma. To form a connected main network, FOLFOX and CAPOX were assumed equally efficacious and combined. In the latest publicly available data, hazard ratios (HRs) of PFS and OS for intent-to-treat (ITT) populations were extracted or reconstructed from Kaplan-Meier curves when not reported. Results: A total of 12 trials (6663 pts) for PFS analysis and 10 trials (6735 pts) for OS analysis representing 8 regimens. Pts were randomly assigned to an experimental arm vs FOLFOX/CAPOX. Pts on 1L nivolumab, pembrolizumab, or truxumab in combination with CX/CAPOX or FOLFOX/CAPOX had significantly reduced risk of disease progression or death vs FOLFOX/CAPOX (Table). Pembrolizumab + FOLFOX/CAPOX had the highest probability of being ranked as the relative efficacy for both PFS (probability: 0.54) and OS (0.36); followed by pembrolizumab + CX (0.27) and pembrolizumab + FOLFOX/CAPOX (0.13) for PFS; and by pembrolizumab + CX/CAPOX (0.3) and nivolumab + FOLFOX/CAPOX (0.24) for OS. Conclusions: This NMA examined the relative benefit of 1L therapies. The results from this combined network on pembrolizumab plus chemotherapy for CLDN18.2+ adenocarcinoma confers a significant PFS and OS benefit, similar to that achieved with PD-1/PD-L1 inhibitors vs chemotherapy plus FOLFOX/CAPOX. Research Sponsor: Astellas Pharma inc.

Pairwise treatment comparisons for PFS and OS with 1L therapies vs FOLFOX/CAPOX.*

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median HR for PFS (95% CI)</th>
<th>Median HR for OS (95% CI)</th>
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<tbody>
<tr>
<td>Zolbetuximab + FOLFOX/CAPOX</td>
<td>0.71 (0.62, 0.82)</td>
<td>0.74 (0.67, 0.89)</td>
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<tr>
<td>Nivolumab + FOLFOX/CAPOX</td>
<td>0.79 (0.70, 0.89)</td>
<td>0.79 (0.70, 0.88)</td>
</tr>
<tr>
<td>Pembrolizumab + CX/CAPOX</td>
<td>0.76 (0.64, 0.86)</td>
<td>0.78 (0.69, 0.88)</td>
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<tr>
<td>Pembrolizumab + CX</td>
<td>0.80 (0.53, 1.20)</td>
<td>0.89 (0.56, 1.48)</td>
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<tr>
<td>FOLFOX + CX</td>
<td>1.18 (0.60, 1.54)</td>
<td>1.35 (0.76, 1.72)</td>
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<tr>
<td>CX</td>
<td>0.84 (0.55, 1.29)</td>
<td>1.15 (0.79, 1.67)</td>
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<tr>
<td>SCC</td>
<td>1.13 (0.84, 1.52)</td>
<td>1.27 (0.96, 1.66)</td>
</tr>
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</table>

*Based on pts in ITT populations regardless of PD-L1 CPS status.

326 Poster Session

FRONTIER: A feasibility study of nivolumab with neoadjuvant CF or DCF, FLOT therapy for locally advanced esophageal carcinoma (JCG01804E)—Primary and short-term efficacy results for cohort E. First Author: Akihide Hashimoto, Takamasa Kariishi, Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan.

Background: The standard neoadjuvant treatment in Japan for resectable locally advanced esophageal squamous cell carcinoma (ESCC) is DTX + CDOP + 5-FU (DCF). In addition, immune checkpoint inhibitors (ICIs) have shown a survival benefit for ESCC and are promising as neoadjuvant treatment for several cancers. We previously reported that neoadjuvant nivolumab + 5-FU + S-1 + cisplatin (Nivo) or nivolumab + pemetrexed (Nivo + Pem) showed promising efficacy for ESCC. However, the efficacy of neoadjuvant treatment and safety of subsequent surgery remain unclear for 5-FU + I-LV + L-OHP + DTX (FLOT), the global standard of care for perioperative esophageogastric adenocarcinoma, plus ICI for ESCC. Methods: JCG01804E (FRONTIER) is a multi-center phase I study designed to evaluate the safety and efficacy of Nivo combined with neoadjuvant chemotherapy in ESCC. The eligibility criteria were histologically proven ESCC staged at cT1N0M0 or cT2N0M0 (8th UICC TNM classification), age 20-75 years, performance status (PS) 0-1, and no prior cancer therapy. The primary endpoint was the incidence of dose-limiting toxicity (DLT) at the initial dose to postoperative day 30. The secondary endpoints included adverse events during the perioperative period and at 30 days and the objective response rate, R0 resection rate, histopathological complete response rate, and completion rate of the protocol treatment including planned chemotherapy as below followed by R0 resection. Results: Of the five study cohorts, patients in cohort E were planned to receive four courses of FLOT+Nivo–5-FU (2600mg/m²), I-LV (200mg/m²), L-OHP (85mg/m²), DTX (50mg/m²), and Nivo (240mg)–on day 1 every 2 weeks. Results: Of the 12 patients enrolled in cohort E (median age [range]: 64.3 [53-71] years, PS 0-1/2; 12/0, clinical stage III/II/III/IV: 4/3/5/0, 4 developed DL (grade 3 mucositis, erythema multiforme, and pneumonitis, n=1 each), 4 grade 5 pneumonitis, n=1), which was within the prespecified range of safety (n ≤ 5). Other grades≥3 adverse events were neutropenia (n=7), leukopenia (n=6), fever, fatigue, febrile neutropenia, rash, elevated amylase, elevated hepatic enzyme, hypotension, and thrombocytopenia (n=1 each) during FLOT + Nivo, and anastomotic leakage (n=1) during the perioperative period. One patient discontinued FLOT due to Nivo due to grade 3 neutropenia. In 14 patients, 10 (71.4%) were pathologic complete responders (pCR), eleven patients (91.7%) completed the protocol treatment and R0 resection rate achieved 91.7% (11/12). In cohort E, the objective response rate in patients with measurable lesion was 0% (0/4). However, 5 patients (41.7%) achieved a pathological complete response (<0.2%) and 8 (69%) achieved a pathological complete response at follow-up. Conclusions: Neoadjuvant FLOT + Nivo followed by surgery for locally advanced ESCC was tolerated and showed promising efficacy. Clinical trial information: ChiCTR2200059976. Research Sponsor: Ono Pharmaceutical Co., Ltd.

328 Poster Session

Chemotherapy and chemoradiotherapy for adenocarcinoma of the esophagus and junction with oligometastases: Results of the TNT-OES-1 trial. First Author: Charlene J. van der Zijden, Department of Surgery, Erasmus MC Cancer Institute, Rotterdam, Netherlands.

Background: Chemotherapy (FLOT) and chemoradiotherapy (CROSS) are effective as far advanced disease in esophageal and junction cancer. Total Neoadjuvant Therapy (TNT) aims to increase efficacy by combining chemotherapy with chemoradiotherapy. Although TNT is increasingly used in rectal cancer, there are no data on combining FLOT and CROSS in esophageal cancer. This study aimed to evaluate the feasibility and safety of the new protocol in combination with chemotherapy for esophageal cancer: the new TNT-OES protocol. Methods: This phase II study included patients with oligometastatic (a maximum of four lesions in up to two organs, excluding lymph nodes) esophageal adenocarcinoma. Patients were treated with four biweekly cycles of FLOT. Response was evaluated by CT-scan 4-6 weeks after completion of FLOT. If patients showed regression or response, and 60% (P0) based on RESIST criteria (v1.1), they received CROSS. Four to six weeks after completion of CROSS, response was assessed by CT-scan, endoscopy with biopsies and endoscopic ultrasonography. The multidisciplinary tumor board discussed whether patients could proceed to four additional cycles of FLOT or local therapy of metastases and/or esophagectomy. Results: Twenty-two patients were included, the majority with a metastatic burden (over 25% of lesions spread (80%) had a single metastatic lesion. 14 of 20 patients (70%) successfully completed the FLOT regimen, four are still in therapy and two patients died. Eleven of 14 patients completed FLOT-CROSS and three patients showed disease progression following FLOT. Toxicity mainly consisted of grade 1-2 leukopenia/neutropenia during FLOT, leading to treatment delay in seven patients. One patient had malaise grade 2. No grade 4 toxicities or treatment delays/discontinuations occurred during CROSS. Following FLOT-CROSS, seven patients underwent four additional cycles of FLOT. Six patients underwent esophagectomy and two of those also underwent local treatment of metastases. A pathologically complete response was seen in two of these six patients (33%). Three of seven patients had a clinically complete response and opted for active surveillance after shared decision making. Three months after completion of FLOT-CROSS, the DCR was 82%. Conclusions: This study showed that sequencing FLOT-CROSS in patients with oligometastatic esophageal adenocarcinoma is feasible and comes with manageable toxicity. We saw promising efficacy, with 24% having a pathologic complete response.

Post Session 330

Tislelizumab plus chemotherapy (chemo) versus placebo plus chemosens as first-line treatment for locally advanced or metastatic gastric and gastroesophageal junction adenocarcinoma: RATIONALE-170 European/North American patient subgroup. First Author: Hendrik-Tobias Arkenau, Sarah Cannon Research, London, United Kingdom

Background: Tislelizumab (TIS), an anti-programmed cell death protein 1 monoclonal antibody, plus chemo, demonstrated significant overall survival (OS) benefit vs placebo (PBO) plus chemo (15.0 vs 12.9 months [mo]; hazard ratio [HR]=0.80, 95% confidence interval [CI]: 0.76, 0.92; P=0.0011) as first-line therapy in patients (pts) with advanced gastric and gastroesophageal junction adenocarcinoma (GC/GEJC). The study was a blinded, global, phase 3 RATIONALE-305 study (NCT03777657). Here we present results from the European/North American (Eu/NA) pts subgroup analysis.

Methods: This double-blind, global, phase 3 study evaluated advanced pts with previously untreated, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced, resectable, or metastatic GC/GEJC, regardless of programmed death-ligand 1 (PD-L1) expression status. Eligible pts were randomized (1:1) to receive TIS 250 mg or PBO intravenously once every 3 weeks plus investigator chosen chemo (5-fluorouracil + cisplatin or capecitabine + oxaliplatin). The primary endpoint was OS in the PD-L1+ patients (with tumor area positivity score >5%) and intent-to-treat (ITT) analysis sets. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), and safety. Results: Of 997 pts enrolled, 249 (25.0%) were from Eu/NA (TIS plus chemo arm, n=125; PBO plus chemo arm, n=124). In the Eu/NA pts subgroup, after a minimum follow-up of 26.6 mo at final analysis, TIS plus chemo resulted in OS improvements vs PBO plus chemo in the PD-L1+ (HR=0.79; CI: 0.60, 0.99; 24 mo OS rates 65.7 vs 46.0%; P=0.015) and PD-L1- (HR=1.07; 24 mo OS rates 27.6% vs 13.6%). TIS plus chemo resulted in favorable PFS vs PBO plus chemo (HR=0.84; CI: 0.63, 1.11), numerically higher ORR (36.0% vs 31.5%), and longer DoR (median 7.5 mo [CI: 4.4, 12.0] vs 5.0 mo [CI: 3.9, 6.7]). Sixty (48.8%) pts in the TIS plus chemo arm vs 51 (40.9%) pts in the PBO plus chemo arm had grade ≥3 treatment-related adverse events (AEs). Sixteen (13.0%) and seven (5.6%) pts discontinued treatment due to TRAEs in the TIS plus chemo and PBO plus chemo arms, respectively. Deaths due to TRAEs occurred in two (1.6%) pts in the TIS plus chemo arm and one (0.8%) pt in the PBO plus chemo arm. Conclusion: Tislelizumab plus chemotherapy is a manageable safety profile in pts in the Eu/NA subgroup with previously untreated, HER2-negative, locally advanced, resectable, or metastatic GC/GEJC. These findings are consistent with the published results in the overall study population. Clinical trial information: NCT03777657. Research Sponsor: Bristol-Myers Squibb.

Post Session 331

Tislelizumab combined with POFI (rinocetan, paclitaxel, oxaliplatin and 5-FU/levoleucovorin) as first-line treatment of advanced gastric gastroesophageal junction adenocarcinoma (AGC): Preliminary results of a single-arm, open-label, phase II trial (SYLT-023). First Author: Yongbo Lin, Department of Gastrointestinal Medical Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Background: Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity and binding specificity for PD-1. Combined with fluoropyrimidine + platinum (XELOX or FP), it is approved in China as first-line treatment of advanced gastric cancer (AGC). Both irinotecan and paclitaxel have also shown antitumor activity in advanced gastric/gastroesophageal junction adenocarcinoma. Conclusions: Our study may demonstrate the consistent incidence of irAEs in pts who received Nivo+Ipi in the real world, compared to the results of the CheckMate 648. Despite of the short time of follow-up period, 1st-line treatment with Nivo+Ipi appeared to be more efficacious than Nivo+Ipi used as a later-line treatment. Our study may demonstrate a manageable safety profile in pts in the Eu/NA subgroup with previously untreated, HER2-negative, locally advanced, resectable, or metastatic GC/GEJC. These findings are consistent with the published results in the overall study population. Clinical trial information: NCT03777657. Research Sponsor: BeGen, Ltd.
Clinical significance of time interval between surgery and adjuvant chemotherapy in patients with gastric cancer after gastrectomy: A population-based cohort study using a nationwide claims database. First Author: Chi Hoon Maeng, Department of Medicine, Division of Medical Oncology-Hematology, Kyung Hee University Hospital, Seoul, South Korea

Background: Adjuvant chemotherapy can reduce recurrence rates by eradicating microscopic metastases which may persist after curative resection. However, the optimal time interval (TI) between the surgery and chemotherapy remains controversial.

Methods: The data were obtained from the NHIS of Korea. We included patients who underwent gastrectomy for gastric cancer between 2013 and 2018. To determine the optimal cut-off point of TI, a restricted cubic spline cox regression model was established, and categorized the population into three groups based on TI: the early group (≤ 20 days), the reference group (21-34 days), and the late group (≥ 35 days) with the reference interval group having the lowest mortality and recurrence. Propensity score matching was performed for each group. The primary outcomes were disease-free survival (DFS) and overall survival (OS).

Results: During the study period, 98,556 patients underwent surgery for gastric cancer. After excluding ineligible participants, 6,602 patients were included in the analysis. The median DFS and OS did not differ significantly between the early and reference groups (p = 0.7285 and p = 0.6056, respectively). In comparison between the late and reference groups, the median DFS was significantly lower in the late group (p = 0.0079). 5-year DFS were 77.6% and 81.3% in the late and reference groups, respectively. Furthermore, the late group showed worse OS than the reference group (p = 0.0326). OS at 5-year were 82.1% and 85.0% in the late and reference groups, respectively. In the multivariable analysis, DFS in the late group retained inferiority (ahr 1.138, 95% CI: 1.009-1.292, p = 0.045). OS showed a worse trend without significance compared to the reference group (ahr 1.138, 95% CI: 0.984-1.317, p = 0.0805).

Conclusions: Adjuvant chemotherapy after gastrectomy in patients with gastric cancer should be initiated within five weeks of surgery. A delay of more than five weeks may have a detrimental effect on the subsequent disease course.

Research Sponsor: National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT); 2021R1F1A1061156.

Impact of adding nivolumab to first-line chemotherapy in patients with advanced gastric cancer. First Author: Mai Utsumi, Osaka Medical and Pharmaceutical University Hospital, Takatsuki, Japan

Background: Nivolumab plus chemotherapy (Niv-Neho) is the standard treatment for advanced gastric cancer based on the results of CheckMate 649 trial and ATTRACTION-4 trial. However, real-world data on the efficacy of Nivo-Cemo are limited. This study aimed to assess the efficacy of Nivo-Cemo in the clinical practice setting by comparing it to chemotherapy alone. Methods: We retrospectively reviewed the medical records of patients with advanced gastric cancer who received palliative chemotherapy in our hospital between 2017 and 2023. The inclusion criteria were as follows: age ≥ 20 years; histologically confirmed advanced unsectetable or recurrent gastric/gastro-esophageal junction adenocarcinoma; HER2 negative or unknown; and no prior treatment. Patients were divided into two groups based on their first-line treatment: the Niv-Neho group and chemotherapy alone (Chemo) group. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) were assessed.

Results: Of 78 patients, 52 patients were in the Chemo group and 26 patients were in the Niv-Neho group. Median age were 69 years (range 30–83) and 67 years (range 39–76) in the Chemo group and Niv-Neho group.Eastern Cooperative Oncology Group performance status (ECOG PS) was 0/1/2 in 18/27/77 patients (35%/52%/13%) in the Chemo group and in 17/81 patients (65%/31%/4%) in the Niv-Neho group. Histological type (intestinal type/diffuse type) was 19/33 (37%/63%) in the Chemo group and 8/18 (31%/69%) in the Niv-Neho group. Combined positive score (CPS) was assessed in 21 patients in the Chemo group. The CPS ≤ 1/1–5/6 was 3 in 3/10 (12%/38%)

In the Chemo group, 28 patients (54%) received anti-PD-1 monotherapy after progression of first-line chemotherapy. The median PFS was 5.7 months in the Chemo group and 6.0 months in the Niv-Neho group (HR 0.89, 95% CI 0.50-1.55, p = 0.66). The median OS was 15.0 months in the Chemo group and 18.6 months in the Niv-Neho group (HR 0.76, 95% CI 0.37-1.53, p = 0.44). The DCR was 50% in the Chemo group and 54% in the Niv-Neho group, while the DCR was 63% and 69%, respectively.

Conclusions: In clinical practice, the addition of nivolumab to chemotherapy tended to provide a survival benefit compared to chemotherapy alone. Research Sponsor: None.

A phase Ib/II study of fruquintinib in combination with SOX and toripalimab as first-line treatment for advanced metastatic gastric/gastroesophageal junction adenocarcinoma (GC/GEJC). First Author: Xiangrui Meng, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background: Immune checkpoint inhibitors (ICls) plus chemotherapy has become the standard first-line regimen for advanced GC/GEJC, but the efficacy still needs to be improved. Fruquintinib is an oral, highly selective VEGFR 1/2/3 inhibitor that has synergistic antitumor effects when combined with ICls/chemotherapy. Additionally, the phase III study (NCT03223376) of fruquintinib combined with paclitaxel in second-line GC/GEJC has achieved positive topline result. Therefore, this study was aimed to evaluate the efficacy and safety of fruquintinib combined with SOX and toripalimab as a first-line therapy in GC/GEJC.

Methods: In this phase Ib/II, open-label trial (NCT05024812), patients (pts) aged 18-75 years who were HER2-negative with no previous anti-tumor therapy were enrolled. The Ib phase included 17 pts achieving 3PR in 6 pts, 4PR in 6 pts, 5PR in 1 pt. The DCR was 100% (16/16). The ORR was 56.3% (9/16), the DCR was 100% (16/16). Pts with PD-L1 CPS 1 were more likely to achieve better responses (4PR in 6 pts, ORR-66.7%). After a median follow-up of 20 months, 1 pt had PD and 2 pts had NS. Median DOR was 3.5 months. Median PFS was 5.7 months and median OS was 15.0 months. The majority of AEs were grade 1/2 events. Grade 3 TRAEs included neutrophil count decreased (11.8%), white blood cell decreased, hypoproteinemia and platelet count decreased (64.3%), anemia (47.7%), and hypertension (46.3%). Grade 4 TRAEs included neutrophil count decreased (6.3%), white blood cell decreased (6.3%), hypoproteinemia (1.3%), and aspartate aminotransferase (1.3%). There were no treatment related deaths in the trial.

Conclusions: Fruquintinib combined with SOX and toripalimab was well tolerated, with encouraging antitumor activity as first-line treatment for advanced metastatic GC/GEJC, especially in pts with CPS ≥ 1. The trial is still recruiting, more data including the potential predictive biomarkers would be further analyzed and reported. Clinical trial notification: NCT05024812. Research Sponsor: None.

Clinical outcomes of argon plasma coagulation for the treatment of gastric low-grade dysplasia. First Author: Hoyoung Wang, Ulsan University Hospital, Ulsan University College of Medicine, Ulsan, South Korea

Background: Argon plasma coagulation (APC) could be considered a treatment modality for small gastric low-grade dysplasia (LGD) instead of endoscopic resection (ER). Our study investigated the clinical outcomes of APC for treating gastric LGD and associated variables with local recurrence. Methods: This study included 911 patients who underwent APC for gastric neoplasms at the tertiary hospital from July 2007 to March 2022 with a minimal follow-up of 12 months. 112 subjects without any information about H. pylori infection status, 164 subjects who underwent APC for salvage therapy, 18 subjects with high grade dysplasia, and 12 subjects with cancer were excluded. Through a retrospective review of medical data, the clinical outcomes and variables associated with the local recurrence were analyzed. Results: A total of 618 patients with LGD (median age of 64 years old) were followed up for a median of 36 months and local recurrence has happened in 21 patients (3.4%). Multivariate analysis showed lesion size (hazard ratio 1.06, 95% confidential interval 1.01–1.12) was associated with the local recurrence. Among 557 lesions smaller than 10 mm, local recurrence was found in 14 cases (2.6%) and local recurrence was in 7 cases (9.5%) of 109 tumors larger than 10 mm (p = 0.004).

Conclusions: In gastric LDLG smaller than 10 mm without scars, APC is a good treatment modality in place of ER. However, when a lesion is larger, APC should be selected carefully with close monitoring. Research Sponsor: None.
Infusional fluorouracil and weekly docetaxel as first-line therapy for gastric cancer with bone marrow metastasis and disseminated intravascular coagulation: A multi-center, phase II trial (Zhen Long). First Author: Jian Xiao, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Background: Gastric cancer (GC) with bone marrow metastasis (BMM) and disseminated intravascular coagulation (DIC) constitute a highly aggressive GC (HAGC) sub-type with distinctive features. The prognosis is poor and most HAGC patients die in weeks without effective treatment. Undue concerns about the myelosuppression mitigate against the application of cytotoxics in HAGC which is characterized by thrombocytopenia. Retrospective analysis showed low dose chemotherapy might relieve the DIC and bring with survival benefit but the standard of care (SOC) has not yet been established without a prospective study available. We completed a multi-center phase II trial evaluating the safety and efficacy of infusional fluorouracil and weekly docetaxel as first-line (1L) treatment for HAGC. Methods: This was a single-arm trial. A Simon’s two-stage optimal design was applied. Eligible cases were 18-75 years old, histologically confirmed GC, established BMM, overt DIC, platelet ≤ 50×10^9/L and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3. Fluorouracil 200mg/m²/d continuous infusion on days 1-21 and docetaxel 25mg/m² on days 1, 8, 15 were given every four weeks. Hematological response (HeR) was defined as the platelet restored to normal range. The primary end point was HeR rate. Secondary end points were time to HeR (TTHeR), one month mortality (OMM), overall survival (OS), adverse events (AEs) and quality of life (Qol).

Results: From Jan 2021 to Sep 2022, 24 HAGC cases from three Chinese centers were enrolled (details shown in table below). 20 HeRs were achieved and the HeR rate was 83.3%. Median TTHeR was 13 days and OMM was 12.5%. Till the data cut-off date (Jul 31, 2023), 3 patients were still alive with a median follow-up of 403 days. The median OS was 242 days. Totally, twelve Grade 3 AEs were recorded in 7 (29.2%) patients, among which stomatitis (4, 16.7%) and anminotransferase elevation (3, 12.5%) were the most frequent. No drug-related grade 4 or 5 AEs were observed. QoL outcomes were significantly improved both during and after the treatment. Conclusions: Anti-cancer treatment is the key point to control DIC of HAGC. The Zhen Long regimen was well tolerated and showed promising efficacy in the 1L setting. It should be considered as the SOC in current practice, but further randomized trials are still needed. Clinical trial information: NCT04547153. Research Sponsor: Wu Jeping Medical Foundation.

Characteristics

- Median age, years (range) 51.5 22-66
- ECOG PS 3 16 66.7%
- PLT < 50×10^9/L 9 37.5%
- Median DIC score (range) 6 3-8
- Previous gastrectomy 9 41.7%
- Adjuvant chemotherapy 9 37.5%
- ECOG PS 2 22 88.9%
- HeR rate, % (95% CI) 83.3% 67.3%-99.4%
- Median TTHeR (range) 13 7-36
- OMM 3 12.5%
- Median OS, days (95% CI) 242 193.2-284.5
- Grade 3 AEs 7 29.2%

Survival outcomes in patients with resectable gastric cancer treated with total neoadjuvant therapy. First Author: Yun Song, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Perioperative chemotherapy is the standard of care for patients diagnosed with advanced gastric cancer. However, the use of total neoadjuvant therapy (TNT), which includes both chemotherapy and chemoradiation, is increasing in other malignancies. The purpose of this study is to determine overall survival (OS) in a contemporary cohort of gastric cancer patients treated with TNT and surgical resection. Methods: Patients diagnosed with microsatellite-stable clinical T1-2 or N+ gastric adenocarcinoma (January 2012 to June 2022) were identified from a prospectively maintained institutional database. Those who underwent staging laparoscopy and received neoadjuvant chemotherapy and chemoradiation therapy, followed by gastrectomy, were included in the study. OS and variables associated with OS were determined using standard statistical methods. Results: Of 203 study patients, the median (interquartile range) age was 61 (50-69.5) years and 50 (24.6%) had tumor involving the gastroesophageal junction. The most common TNT sequence was chemotherapy followed by chemoradiation, which was utilized in 173 (85.2%) patients. The chemotherapy regimen typically given was fluorouracil and oxaliplatin in 149 (73.4%) patients. The most common radiation dose was 45 Gy in 25 fractions (169 [83.3%] patients), with 18 (8.9%) patients receiving 30 Gy in 10 fractions. One hundred ninety-seven (97.0%) patients completed all their planned neoadjuvant therapy. Surgical resection included total gastrectomy in 108 (53.2%), adjacent organ resection in 24 (11.8%), and extended (D1+/D2) lymphadenectomy in 193 (95.1%) patients. Pathologic complete response was achieved (pCR) in 32 (15.8%) patients. The median OS was 8.4 (95% CI 6.2-10.5) months with a median follow-up of 403 days. The median OS was 242 days. Totally, twelve Grade 3 AEs were recorded in 7 (29.2%) patients, among which stomatitis (4, 16.7%) and anminotransferase elevation (3, 12.5%) were the most frequent. No drug-related grade 4 or 5 AEs were observed. QoL outcomes were significantly improved both during and after the treatment. Conclusions: Anti-cancer treatment is the key point to control DIC of HAGC. The Zhen Long regimen was well tolerated and showed promising efficacy in the 1L setting. It should be considered as the SOC in current practice, but further randomized trials are still needed. Clinical trial information: NCT04547153. Research Sponsor: Wu Jeping Medical Foundation.

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Infusional fluorouracil and weekly docetaxel as first-line therapy for gastric cancer with bone marrow metastasis and disseminated intravascular coagulation: A multi-center, phase II trial (Zhen Long). First Author: Jian Xiao, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Background: Gastric cancer (GC) with bone marrow metastasis (BMM) and disseminated intravascular coagulation (DIC) constitute a highly aggressive GC (HAGC) sub-type with distinctive features. The prognosis is poor and most HAGC patients die in weeks without effective treatment. Undue concerns about the myelosuppression mitigate against the application of cytotoxics in HAGC which is characterized by thrombocytopenia. Retrospective analysis showed low dose chemotherapy might relieve the DIC and bring with survival benefit but the standard of care (SOC) has not yet been established without a prospective study available. We completed a multi-center phase II trial evaluating the safety and efficacy of infusional fluorouracil and weekly docetaxel as first-line (1L) treatment for HAGC. Methods: This was a single-arm trial. A Simon’s two-stage optimal design was applied. Eligible cases were 18-75 years old, histologically confirmed GC, established BMM, overt DIC, platelet ≤ 50×10^9/L and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 3. Fluorouracil 200mg/m²/d continuous infusion on days 1-21 and docetaxel 25mg/m² on days 1, 8, 15 were given every four weeks. Hematological response (HeR) was defined as the platelet restored to normal range. The primary end point was HeR rate. Secondary end points were time to HeR (TTHeR), one month mortality (OMM), overall survival (OS), adverse events (AEs) and quality of life (Qol).

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Initial safety assessment of the endoscopically injected oncolytic virus OBP-301 in medically inoperable esophageal cancer: NRG-GI007. First Author: Geoffrey Yuyat Ku, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Definitive chemoradiation (CRT) is a standard-of-care for patients (Pts) with medically inoperable esophageal cancer (EC). The NRG/RTOG 0436 study of cisplatin/paclitaxel and RT (50.4 Gy/28 fractions) for Pts with medically inoperable EC, Ptss receive 1-2 mL of intratumoral OBP-301 1x10^6 viruses/mL via endoscopic delivery 3 days prior to and then at days 12 and 26 of CRT. The primary endpoint is dose-limiting toxicity (DLT), defined as adverse events (AEs, by CTCAE v5) definitely or probably attributed to OBP-301 that meet either of the following: (1) leading to a >14-day cumulative delay in CRT or (2) any grade ≥ 3 AE EXCEPT: grade 3 nausea/vomiting, grade 3 esophagitis or dehydration, first occurrence of grade 3/4 neutropenia, or grade 3/4 thrombocytopenia. Initially, 6 evaluable Pts (eligible and started protocol treatment) are enrolled. If protocol defined DLT occurs in ≤ 1 of 6 Pts, the dose will be deemed safe and an expansion cohort of 9 more will be enrolled to further safety and obtain a preliminary assessment of complete response. If ≥ 2 Pts have a DLT then one de-escalated OBP-301 dose will be assessed. Results: From June 2020 to April 2023, 6 evaluable Pts were enrolled. Median age was 73.5 years, all male. 5 Pts had adenocarcinoma and 1 squamous cell carcinoma; 3 Pts had node-negative disease. All Pts received all planned OBP-301 injections, along with 50.4 Gy RT. Four out of 6 Pts received all 5 weekly doses of chemo for > 85% of planned total dose, and 2 got 4 weekly doses for > 70% of planned total dose. No Pt experienced a treatment delay. The following treatment-related (attributed as definitely, probably, or possibly related to CRT and/or OBP-301) grade ≥ 3 AEs were reported across 3 Pts: decreased neutrophil count (3 Pts), decreased lymphocyte count (2 Pts), and fever and fatigue (1 Pt each). There were 4 Pts with AEs reported as definitely or probably related to OBP-301, all grade ≥2. No DLT occurred. Conclusions: No DLTs in the 6 evaluable Pts were observed and it is concluded that the initial OBP-301 dose level is safe. NRG-GI007 was reopened on August 7, 2023 to the dose expansion cohort. Full toxicity and treatment data will be presented. 1. Eur J Cancer 2021; 153:98. Clinical trial information: NCT04391049. Research Sponsor: U10CA180822 (NRG SDMC); U10CA180888 (NRG Operations) and U24CA180803 (IROC) from the National Cancer Institute (NCI); Oncolytics.

Advantages of robotic surgery for advanced gastric cancer in short-term outcomes: A single-center retrospective study using propensity score matching. First Author: Masaru Komatsu, National Cancer Center Hospital East, Kashiwa, Japan

Background: The advantages of robotic gastrectomy (RG) for gastric cancer are being demonstrated. However, there are few reports that have focused on advanced gastric cancer and examined the advantages of RG for laparoscopic gastrectomy (LG). We conducted the following study to clarify the advantages of RG for advanced gastric cancer. Methods: This single-center retrospective study reviewed the clinical data of 1531 patients who underwent either RG or LG from 2014 to 2023. 473 patients were with clinical diagnoses as having advanced gastric cancer. They were divided into the RG group (n = 143) and the LG group (n = 330). Propensity score matching was employed to adjust the background of the two groups, as covariates of age, gender, BMI, surgical method (distal gastrectomy/total gastrectomy), stage (early cancer/advanced cancer), and presence or absence of preoperative chemotherapy. Then, the treatment results were compared and examined. Results: 130 patients in each group were extracted by propensity score matching. There were no significant differences in age, gender, and ECOG-PS between the two groups. Compared to the LG group, the RG group had more cases with deeper invasion depth (p=0.01, 0.04, more D2 dissection (96.9 vs 88.5%, P = 0.01), and longer operative time (359.5 vs 294.5 min, P < 0.01). The number of retrieved lymph nodes was larger (49.5 vs 44, P =0.01) in the RG group. Importantly, in the RG group, there were fewer complications with Clavien-Dindo classification ≥Grade II (11.5 vs 21.5%, P = 0.04) and CD classification ≥Grade III (0.8% vs 6.9%, P = 0.01). Postoperative hospital stay was shorter (8 vs 9 days, P = 0.01) in the RG group. Conclusions: RG for advanced gastric cancer has the potential to reduce complications compared to LG. Long-term survival outcomes should be investigated. Research Sponsor: None.
First-line pembrolizumab (pembro) plus chemotherapy (chemo) for advanced gastroesophageal junction cancer (GEJC) and esophageal adenocarcinoma (EAC): Analysis of KEYNOTE-590 and KEYNOTE-859 by tumor type. First Author: Zev A. Wainberg, David Geffen School of Medicine at UCLA, Los Angeles, CA

**Background:** First-line (1L) treatment of GEJC and EAC is similar to that for gastric adenocarcinoma, based on evidence from 2 large phase 3 gastric and esophageal cancer trials. The phase 3 KEYNOTE-590 trial (NCT03681791) showed 1L pembro + chemo significantly improved OS and PFS in pts with esophageal cancer. The phase 3 KEYNOTE-859 trial (NCT03675737) showed 1L pembro + chemo significantly improved OS, PFS, and ORR in pts with HER2-negative gastric cancer or GEJC. This post hoc, exploratory analysis was conducted to examine the efficacy of 1L pembro + chemo in the GEJC and EAC subgroups of KEYNOTE-590 and the GEJC subgroup of KEYNOTE-859. **Methods:** Pts with untreated advanced EAC or Swet tumor type 1 adenocarcinoma of the GEJC (KEYNOTE-590) or HER2-negative GEJC adenocarcinoma (KEYNOTE-859), measurable disease per RECIST v1.1, and ECOG PS 0 or 1 were evaluated. In both studies, pts were randomly assigned 1:1 to receive pembro 200 mg iv q3w or b/v every 3 wk (Q2W) for 35 cycles, each with chemo (5-fluorouracil + cisplatin [FP] in KEYNOTE-590; FP or capecitabine + oxaliplatin in KEYNOTE-859). Efficacy endpoints for this analysis were OS and PFS (per RECIST v1.1) by blinded independent central review) by tumor type. Database cutoff was May 2020, for KEYNOTE-590 and July 1, 2022, for KEYNOTE-859. Results: Overall, 201 pts from KEYNOTE-590 (99 pembro + chemo; n=102 pbro + chemo) with GEJC or EAC and 334 pts from KEYNOTE-859 (n=149 pembro + chemo; n=185 pbro + chemo) with GEJC were included. In KEYNOTE-590, 91 pts had GEJC only (n=41 pembro + chemo; n=50 pbro + chemo) and 169 (n=82 pembro + chemo; n=87 pbro + chemo) had GEJC + EAC + CPS ≥1. In KEYNOTE-859, 287 pts (n=123 pembro + chemo; n=164 pbro + chemo) had GEJC + CPS ≥1. Demographic and baseline characteristics were well balanced. **Results:** Median time from randomization to database cutoff for pts with GEJC and EAC was 23.5 mos (range, 15.3-33.6) in KEYNOTE-590 and 25.8 mos (range, 12.4-43.0) in KEYNOTE-859. Efficacy outcomes by tumor type are shown in the Table. **Conclusions:** Consistent with results from the ITT populations of KEYNOTE-590 and KEYNOTE-859, 1L pembro + chemo provided clinically meaningful and improved OS and PFS in pts with untreated advanced GEJC and EAC. These data support the use of 1L pembro + chemo for pts with advanced GEJC and EAC. Clinical trial information: NCT03681791 and NCT03675737.

Research Sponsor: Merck & Co., Inc., Rahway, NJ, USA.

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Safety and efficacy of nanosomal docetaxel lipid suspension (NDLS) in patients with advanced gastric adenocarcinoma. First Author: Vikas S. Ostwal, Tata Memorial Hospital (HBNI), Mumbai, India

**Background:** Nanosomal docetaxel lipid suspension (NDLS) was developed to overcome toxicity issues associated with conventional docetaxel. Docetaxel, cisplatin, 5-fluorouracil (5-FU) plus docetaxel or modified docetaxel (mDCF) is one of the recommended first-line regimens for patients with metastatic gastric adenocarcinoma (GAC). However, majority of the patients experienced grade 3/4 toxicities with DCF regimen using conventional docetaxel. The present study evaluated the safety and efficacy of NDLS-based mDCF regimen in patients with metastatic GAC.

**Methods:** In this multicentric, open-label, clinical trial, patients with previously untreated metastatic GAC were enrolled. Patients received either mDCF (NLS 40 mg/m² on day 1, DCF 40 mg/m² on days 2 and 3, 5-FU 400 mg/m² bolus on day 2, DCF:5). At week 18, ORR was 57.9% & DCR was 81.6% in mITT analysis for efficacy evaluation (mDCF: 33, DCF:5). At week 18, ORR was 57.9% & DCR was 81.6% in mITT analysis. In the per-protocol population (n=26), DCR was 61.5% & (n=18) weeks (mDCF: 63.6%, DCF: 50%). Safety included all thirty-two patients. Any grade adverse events (AEs) were reported in 90.4% (n=47) of the patients; with 40.4% experiencing grade 3/4 AEs. All-grade AEs reported in <10% of the patients included anemia, neutropenia, abdominal pain, diarrhea, nausea, vomiting, fatigue, mucositis, decreased appetite, peripheral neuropathy; with majority of AEs being grade 1/2. Most common grade 3/4 AE was neutropenia, observed in 17.3% (n=9 patients) in mDCF: 14%, DCF: 33.3%. **Conclusions:** NDLS-based regimens demonstrated efficacy & improved safety profile in the treatment of metastatic GAC. Clinical trial information: CTRI/2018/01/014450. Research Sponsor: Intas Pharmaceuticals Limited, Ahmedabad, Gujarat, India.

**Efficacy outcomes.**

<table>
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<th>Parameter</th>
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<th>mDCF (n=23)</th>
<th>DCF (n=5)</th>
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<tr>
<td>CR, n (%)</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>17 (44.2)</td>
<td>21 (55.3)</td>
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<td>SD, n (%)</td>
<td>9 (23.7)</td>
<td>8 (22.2)</td>
<td>2 (40.0)</td>
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<tr>
<td>ORR, n (%)</td>
<td>20 (52.6)</td>
<td>22 (52.6)</td>
<td>17 (53.3)</td>
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<td>Median F(PS) (months), 95% CI</td>
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<td>Female, n (%)</td>
<td>16 (42.1)</td>
<td>11 (44.2)</td>
<td>9 (33.3)</td>
</tr>
</tbody>
</table>
| First Author: Vikas S. Ostwal, Tata Memorial Hospital (HBNI), Mumbai, India

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349 Poster Session
Neoadjuvant toripalimab plus CapeOX in patients with localized dMMR/MSI-H gastric or esophagogastric junction adenocarcinoma (GC/EGJC): Results from the cohort C of phase II NICE trial.

**Background:** Gastric cancer (GC) and esophagogastric junction adenocarcinoma (EGJC) are high mortality cancers. Neoadjuvant chemoradiation therapy (cCRT) might boost antitumor immunity. The current study aims to evaluate the safety and efficacy of peroperative immunotherapeutic regimen with CapeOX in dMMR/MSI-H tumors.

**Methods:** NICE trial was a multicenter, multi-cohort phase II trial (NCT04744649) investigating the safety and efficacy of toripalimab combined with CapeOX regimen as perioperative treatment in dMMR/MSI-H GC/EGJC (cohort A: CapeOX, cohort B: toripalimab, cohort C: CapeOX plus toripalimab). Main endpoints included the duration of response (DoR), disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety. AEs were collected during the perioperative treatment and after surgery, with the median follow-up of 6.4 months (range: 2.9 to 24.6 months).

**Results:** A total of 36 pts were enrolled and received treatment between Dec 4, 2020 and Apr 8, 2023. 35 pts were evaluable for tumor response. The median age was 63 years (range: 28 to 81 years). The primary endpoint was objective response rate (ORR) per RECIST v1.1, secondary endpoints included the duration of response (DoR), disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety. A total of 36 pts were enrolled and received treatment between Dec 4, 2020 and Apr 29, 2023. 35 pts were evaluable for tumor response. The median age was 63 years (range: 28, 78), with 30 pts (83.3%) were male. 13 pts (36.1%) had 4 cycles therapy preoperatively and one patient completed 2 cycles therapy because of AEs. None had disease progression, while one achieved a complete clinical response at radiology and endoscopy and refused surgery and the other 14 pts underwent resection. The 90 resection rate was 100% (14/14). The 1-year OS was 89.9% (95% CI 75.8% to 97.5%). Median follow-up duration was 6.4 months (range: 2.9 to 24.6 months). Of the Stage II patients (n=73), 7 cases (9.5%) had recurrent disease, while 5 cases (25%) in the Stage III group (n=20) experienced recurrence. Recurrence-Free Survival (RFS) rates at 1 year, 3 years, and 5 years were 92.0% (95%CI 86.5 to 97.9), 84.7% (95%CI 76.4 to 93.9%), and 78.6% (95%CI 65.8 to 94.0%), respectively. A total of 80 patients (86%) completed the adjuvant 3-weekly TS-1 treatment for 1 year or 16 courses, while 25 patients (26.9%) completed the treatment with dose reductions. Adverse events, primarily Grade 1 or 2 diarrhea (28%) and nausea (20%), were manageable. Conclusions: The 3-weekly TS-1 regimen as adjuvant therapy exhibited favorable efficacy and tolerable toxicity in AGC patients. These findings suggest the need for further investigation of this regimen in future clinical studies. Research Sponsor: None.

350 Poster Session
Evaluation of the efficacy and safety of a 3-weekly TS-1 regimen as adjuvant therapy for stage II and III advanced gastric cancer: A pilot study.

**Background:** Neoadjuvant therapy for stage II and III advanced gastric cancer (AGC) is essential in improving patient outcomes. The standard therapy, TS-1 at 80 mg/m2/day for 4 weeks with a 2-week rest, is recommended for 1 year or 8 courses. This study investigates the efficacy and safety of a 3-weekly adjuvant TS-1 regimen in AGC patients.

**Methods:** We conducted an analysis of 93 patients who underwent gastrectomy with LGY lymphadenectomy and initiated a 3-weekly adjuvant TS-1 regimen between February 2017 and May 2022. The novel regimen consisted of TS-1 at 80 mg/m2/day for 2 weeks, followed by a 1-week rest, with a treatment goal of 1 year or 16 courses.

**Results:** Among the 93 patients, 12 (13%) experienced disease recurrence during a median follow-up of 24.6 months (range: 4.2 to 63.6 months). For the Stage II patients (n=73), 7 cases (9.5%) had recurrent disease, while 5 cases (25%) in the Stage III group (n=20) experienced recurrence. Recurrence-Free Survival (RFS) rates at 1 year, 3 years, and 5 years were 92.0% (95%CI 86.5 to 97.9), 84.7% (95%CI 76.4 to 93.9%), and 78.6% (95%CI 65.8 to 94.0%), respectively. A total of 80 patients (86%) completed the adjuvant 3-weekly TS-1 treatment for 1 year or 16 courses, while 25 patients (26.9%) completed the treatment with dose reductions. Adverse events, primarily Grade 1 or 2 diarrhea (28%) and nausea (20%), were manageable. Conclusions: The 3-weekly TS-1 regimen as adjuvant therapy exhibited favorable efficacy and tolerable toxicity in AGC patients. These findings suggest the need for further investigation of this regimen in future clinical studies. Research Sponsor: None.

351 Poster Session
Camrelizumab plus apatinib and SOX as first-line treatment in patients with alpha-fetoprotein–producing gastric or gastroesophageal junction adenocarcinoma: A single-arm, multi-center, phase 2 trial. First Author: Yakan Wang, Key Laboratory of Cancerogenicity and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Institute, Haidian District, Beijing, Beijing, China

**Background:** Patients (pts) with AP-producing G/GEJC adenocarcinoma generally respond poorly to first-line standard chemotherapy. We aimed to assess the efficacy and safety of first-line camrelizumab plus apatinib given concurrently with chemotherapy, followed by camrelizumab plus apatinib in AP-producing G/GEJC adenocarcinoma pts. In this open-label, single-arm, multi-center, phase 2 trial (NCT04609176), pts aged ≥18 years, clinical stage III-IV, unreacted/recurrent or metastatic G/GEJC adenocarcinoma with no prior systemic therapy, serum AFP > 2×ULN or AP positive by the IHC staining method were enrolled. Pts received 4 cycles of standard 5-FU plus oxaliplatin (SOX) and camrelizumab (200mg, iv, d1, q3w) plus apatinib (250mg, po, qd). Pts without disease progression then continued to receive camrelizumab plus apatinib for up to 24 months, or until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1, secondary endpoints included the duration of response (DoR), disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety. Results: A total of 36 pts were enrolled and received treatment between Dec 4, 2020 and Aug 4, 2023. 35 pts were evaluable for tumor response. The median age was 63 years (range: 28, 78), with 30 pts (83.3%) were male. 13 pts (36.1%) presented with GEJ. 34 pts (94.5%) were diagnosed with stage IV. 28 pts (75.0%) had distant metastasis. The median follow-up duration was 6.4 months (range: 2.9 to 24.6 months). Of the Stage II patients (n=73), 7 cases (9.5%) had recurrent disease, while 5 cases (25%) in the Stage III group (n=20) experienced recurrence. Recurrence-Free Survival (RFS) rates at 1 year, 3 years, and 5 years were 92.0% (95%CI 86.5 to 97.9), 84.7% (95%CI 76.4 to 93.9%), and 78.6% (95%CI 65.8 to 94.0%), respectively. A total of 80 patients (86%) completed the adjuvant 3-weekly TS-1 treatment for 1 year or 16 courses, while 25 patients (26.9%) completed the treatment with dose reductions. Adverse events, primarily Grade 1 or 2 diarrhea (28%) and nausea (20%), were manageable. Conclusions: The 3-weekly TS-1 regimen as adjuvant therapy exhibited favorable efficacy and tolerable toxicity in AGC patients. These findings suggest the need for further investigation of this regimen in future clinical studies. Research Sponsor: None.
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**Poster Session**

Preliminary results of surufatinib (Suru) plus standard chemotherapy (ChT) as second line (2L) treatment of advanced gastric cancer (aGC): A single-arm phase 2 clinical trial. First Author: Ting Han, Department of Oncology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

**Background:** Limited options are available for aGC patients who have failed first line (1L) systemic treatment, and single-agent ChT with paclitaxel (Pacl) or irinotecan (Ir) remains the mainstay. Recent studies have suggested improved efficacy with the combination of ChT and antiangiogenic agents in the 2L setting. Suru is a tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1 and CSF-1R. This trial is aimed to evaluate the efficacy and safety of Suru plus Pacl or Ir as 2L treatment for aGC.

**Methods:** This single-arm, single center, phase 2 trial was designed to enroll up to 35 histologically confirmed HER2-negative aGC patients with evaluable disease who failed 1L ChT with or without immunotherapy (II). Eligible patients were administered 21-day cycles with Pacl (250mg/m², po, qd) or Ir (150mg/m², iv, qd) in 2L chemotherapy after progression (PD) of their 1L ChT. Treatment continued until PD, until intolerable toxicity, PD, or death. The primary endpoint was ORR (per RECIST v1.1), and secondary endpoints included DCR, PFS, OS, and safety. Results: As of Sep 11, 2023, 15 patients were enrolled, and 6 patients remained on treatment. The median follow-up time was 5.77 (95% CI: 3.37–10.13) months. Among all patients, the median age was 66 (range: 33–76) years, 14 (93.3%) were male, and 14 (93.3%) had an ECOG PS of 1. Ten (66.7%) patients had received prior anti-PD-1 antibodies, and all 15 patients received Pacl as the standard ChT. All 15 patients were evaluable for tumor response, with 5 PR, 9 SD, and 1 PD as their best overall response (BOR). The ORR and DCR were 33.3% and 93.3%, respectively. The median PFS was 5.23 months, while the OS data was immature yet. The ORR, DCR and PFS seemed comparable between patients with and without prior II. In terms of safety, the combined treatment was generally well tolerated, treatment-related grade 3/4 adverse events included neutropenia (6, 40%), leukopenia (1, 6.7%), lymphopenia (1, 6.7%), and proteinuria (1, 6.7%). There were no treatment-related severe adverse events or treatment-related deaths. Conclusion: These results suggested promising anti-tumor activity and a manageable safety profile of Suru plus Pacl in 2L treatment of aGC. The trial is still ongoing, and more data will be disclosed in the future. Clinical trial information: ChiCTR2000065336. Research Sponsor: HUTCHMED.

**Table:**

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<tr>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (33.3)</td>
<td>3 (30.0)</td>
<td>2 (40.0)</td>
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<tr>
<td>SD</td>
<td>9 (60.0)</td>
<td>6 (60.0)</td>
<td>3 (60.0)</td>
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<tr>
<td>PD</td>
<td>1 (6.7)</td>
<td>1 (10.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>33.3 (11.8–61.6)</td>
<td>30.0 (6.7–65.2)</td>
<td>40.0 (5.5–85.3)</td>
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<tr>
<td>DCR, % (95% CI)</td>
<td>93.3 (68.7–99.8)</td>
<td>90.0 (55.5–99.7)</td>
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<td>mPFS, mo (95% CI)</td>
<td>5.23 (3.67–6.37)</td>
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**356**

**Poster Session**

HLX22 plus XELOX for first-line treatment of HER2-positive locally advanced or metastatic gastric/gastric cancer (G/GC) cancer: A randomized, double-blind, multinational, phase 3 study. First Author: Jin Li, Department of Medical Oncology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China

**Background:** Gastric/gastroesophageal junction (G/GJ) cancer represents a global healthcare challenge. With more than 1 million new cases estimated in 2020, it ranked fifth among all cancers. G/GC is a heterogeneous disease treated in around 30% of patients with G/GJ cancer cases. Despite the improved overall survival with trastuzumab plus chemotherapy, the prognosis remains unsatisfactory, and thus more effective treatments are needed. This study aimed to evaluate the combination of HLX22 (a novel HER2 monoclonal antibody), HLX02 (a trastuzumab biosimilar), and XELOX as first-line chemotherapy for patients with G/GJ cancer in the first-line setting. The study was unblinded 3 months after the last patient was enrolled. Patients with locally advanced or metastatic HER2-positive G/GJ cancer and had not received prior systemic antimtumor therapy were enrolled. Two parallel groups of 2 parts; current report will focus on Part 1. 1) Part 1: 1:1 to receive HLX22 25 mg/kg + HLX02 + XELOX (group A), HLX22 15 mg/kg + HLX02 + XELOX (group B), or placebo + HLX02 + XELOX (group C) in 3-cycle weeks. Primary endpoints were PFS and ORR assessed by IRRC per RECIST v1.1. Secondary endpoints included other efficacy measures and safety. Results: As of July 20, 2023 (data cutoff), 53 patients were randomized to group A (n=18), B (n=17), and C (n=18), and were followed up for a median of 14.4 months. 43 (80.3%) patients were male. Main efficacy results are presented in Table. Table assessments reported in Table were performed by IRRC. Treatment-related adverse events (TRAEs) occurred in 18 (100.0%), 16 (94.1%), and 17 (94.4%) patients in the respective groups. Serious TRAEs were observed in 5 (27.8%) patients in group A, 1 (5.9%) in group B, and 1 (5.6%) in group C. Only 1 (5.6%) patient in group C had grade 5 TRAE. Conclusion: Adding HLX22 to HLX02 + XELOX improved survival and antitumor response in patients with HER2-positive G/GJ cancer in the first-line setting, with a manageable safety profile. Clinical trial information: NCT04498813. Research Sponsor: Shanghai Henlius Biotech, Inc.
Surufatinib plus sintilimab in patients with advanced gastric/ gastroesophageal junction adenocarcinoma (GC/GEJC): A single-arm, open-label, single-center phase II trial. First Author: Dong-Sheng Zhang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China

**Background:** Anti-PD-1 antibodies plus chemotherapy have become the standard first-line treatment for advanced GC/GEJC with CPS score ≥ 5. However, GC/GEJC still has dismal survival outcomes. The current treatment regimen could be subdivided into 20-30% who achieve a response through PD-1 inhibitor targeting VEGFR1-3, FGFR and CSF-1R combined with anti-PD-1 antibodies have synergistic antitumor effects by modulating tumor immune microenvironment. Therefore, a phase II trial to evaluate surufatinib plus sintilimab in patients (pts) with advanced GC/GEJC was conducted. Here we report the results of part A of this trial. Methods: This single arm, open-label, single center phase II trial consisted of two parts: part A (second-line therapy) and part B (first-line therapy). In part A, pts aged 18-75 years who were HER2-negative, failed first-line standard therapy, and immune checkpoint inhibitor therapy naive were enrolled. Part A included safety run-in and dose expansion stages. Six pts in the safety run-in received surufatinib at 250mg once daily as starting dose, in combination with a fixed dose of sintilimab (200 mg, d1, q3w). If more than 1 DLT occurred in stage I, the recommended dose of surufatinib for stage 2 (N=11) would be escalated to 250 mg, otherwise would maintain as 250 mg. The primary endpoint was ORR per RECIST v1.1. Secondary endpoints included DOR, PFS, OS and safety. If the ORR of part A was ≥ 30%, the trial would proceed to Part B (N=44), further evaluating this combination treatment in previously untreated advanced GC/GEJC.

**Results:** At data cutoff on 8/10/2023, 16 pts (6 in safety run-in; 10 in dose expansion) were enrolled in part A. The median age was 56 years; 75% male; 69% with ECOG PS 1. Peritoneum (56%) was the most common metastatic site. No DLTs were observed in the safety run-in stage, so the recommended dose of surufatinib for dose expanding stage was 250 mg. Among the 16 pts evaluable for tumor response, 6 pts achieved PR, 4 pts achieved SD. The confirmed ORR was 43.8% (95% CI: 24.6-62.5%), with 9 (56.3%) pts achieving complete response (CR) and 7 (43.8%) pts achieving partial response (PR). The most common grade 3-4 TEAEs reported by parts A and B were seen with at least one SAE. Perioperative complications resulted in overall 7 SAEs (1 in Arm A and 6 in Arm B). One postoperative mortality (grade 5) was documented in Arm A. Arm B showed no grade 5 SAEs. No serious adverse event caused no patient to withdraw from the study. Conclusions: The results showed surufatinib plus sintilimab acquired preclinical efficacy and manageable safety profile as the second-line treatment for advanced GC/GEJC. Part B is ongoing, and more data analysis will be reported further. Clinical trial information: NCT05235906. Research Sponsor: None.

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Flot compared to FOLFOX/EXELO as a neoadjuvant chemotherapy in locally advanced gastric cancer: Experience of two clinics. First Author: Nikolay Semenov, SBHI Moscow Scientific and Practical Center named after A.S. Logino of DHH, Moscow, Russian Federation.

**Background:** The optimal regimen of neoadjuvant chemotherapy (NCT) in locally advanced gastric cancer (GC) remains controversial, especially whether triplet (FLOT) or duplet (FOLFOX/EXELO) regimen is superior since escalation does not always lead to significant clinical improvement. The aim of this study is to assess efficacy of triplet and duplet chemotherapy regimens as a neoadjuvant approach in locally advanced GC via retrospective data. **Methods:** We queried the data for 334 patients with locally advanced GC (ct2-4 or cT4) diagnosed in 2016–2023 by administered with multi-agent NCT: FLOT or XELO/FOFOX. The primary endpoints were the ratio of patients with disease progression on NCT, rates of ypN0, and rates of pathological complete response (pCR). Secondary endpoints included progression free survival (PFS) and overall survival (OS).

**Results:** 156 patients (out of total 334 included in the study) received duplet NCT (FOLFOX/EXELO, 8/6 cycles respectively). 61.5% were males, median age was 64.4 (range 21.3-85.4) years. 88.2% had cT3-4, and 22.4% had locally advanced gastroesophageal junction (GEJ) adenocarcinoma. 177 patients were treated with triple NCT (FLOT, 8 cycles), 62.1% were males, median age was 59.9 years, 89.2% had ct3-4, and locally advanced GEJ adenocarcinoma was diagnosed in 21.0%. At a median follow up of 34.7 months (mth) using FLOT regimen as NCT was associated with better clinical outcomes. The ratio of patients who have progressed on NCT was 21.5% and 31% in triplet and duplet arms, respectively (p=0.098). Rates of ypN0 were 50.5% in FLOT arm and 43.7% in XELO/FOXELO arm (p=0.36). pCR was achieved in 8.2% and 6.3% in FLOT and XELO/FOXELO arms, respectively (p=0.59). Median PFS was 20.3 mth in FLOT arm and 17.5 mth in XELO/FOXELO arm (p=0.012). Median OS was not reached (NR) for triplet arm and was 25.1 mth for duplet arm (p=0.003). Patients who conversed resectable disease had median PFS of 34.5 and 23.1 months for FLOT and XELO/FOXELO arms (p=0.024). Median OS in these subgroups was NR and 57.0 mth (p<0.003). **Conclusions:** We report that triplet regimen (FLOT) in comparison with duplet (FOLFOX/EXELO) regimen is the more favorable option as a neoadjuvant setting in locally advanced gastric cancer. FLOT NCT is associated with increased ypN0, pCR and shows statistically significant difference in PFS and OS. Research Sponsor: None.
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366 Poster Session

Updated pooled analyses of first-line anti-PD1/PD-L1 inhibitors plus chemotherapy in advanced esophageal squamous cell carcinoma. First Author: Mahnaz Vahed, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Advanced and metastatic esophageal squamous cell carcinoma (ESCC) patients have limited treatment options and poor prognosis. Recently, several studies demonstrated the clinical benefit of combining immune checkpoint inhibitors (ICI) and chemotherapy (CT), leading to its approval in the first-line setting. Since then, efforts have been made to identify the patients who may benefit the most or not from the combination of ICI plus CT. Methods: We searched PubMed, Scopus, and the Cochrane Library for randomized clinical trials investigating first-line ICI plus chemotherapy (CT) for advanced or metastatic ESCC patients. Outcomes of interest included: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and OS according to gender, PD-L1 expression (≤ 1% / > 1%), and PD-L1 CPS (≤ 10 / > 10). We used I2 statistics to assess heterogeneity, and the fixed-effect model was used to pool studies. Results: Eight studies were included with 4,702 patients. Of them, most had an ECOG 0 or 1, and were younger than 65 years (62%), male (77%), and Asian (78%). Metastatic disease was diagnosed in 75% of patients. ICI plus CT was administered to 58%, and 43% received CT +/- placebo. Median follow-up ranged from 7.1 to 22.6 months. ICI plus CT significantly improved all efficacy outcomes compared to CT alone: decreasing the risk of death by 32% (HR for OS: 0.68, 95%CI 0.63-0.74; p < 0.00001); reducing the risk of progression or death by 38% (HR for PFS: 0.62, 95%CI 0.58-0.67; p < 0.00001); and increasing the objective response rate (risk difference: 0.17; 95%CI 0.14-0.20; p < 0.00001). A survival benefit was seen across all subgroup analyses, but it was significantly higher in patients with PD-L1 ≥ 1% compared to those with PD-L1 < 1%, (reduction in the risk of death of 38% versus 22%, respectively, p < 0.03). OS was not significantly different between males versus females, or PD-L1 CPS < 10 versus CPS ≥ 10. Conclusions: Our large systematic review and meta-analysis support the efficacy and survival benefit of ICI plus CT as first-line therapy for all ESCC patients, regardless of gender or PD-L1 expression. Research Sponsor: None.

367 Poster Session

A multi-centre review of the efficacy of re-challenge with platinum doublet in patients with oesophagogastric cancer treated with first-line trastuzumab and chemotherapy. First Author: Jamie Weaver, Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom

Background: HER2 amplification or overexpression is seen in 15-20% of metastatic oesophagogastric cancers. The ToGA trial showed an OS benefit for the use trastuzumab with platinum and fluoropyrimidine combination therapy (T-FP) in the first line setting. Second line trials of targeted agents have been disappointing with poor response rates and the current standard of care is paclitaxel and ramucirumab in combination. A recent phase 2 trial showed no OS benefit to continuing trastuzumab with second line chemotherapy but data regarding the efficacy of treatment beyond progression with re-introduction of first line chemotherapy (platinum and fluoropyrimidine) is limited and conflicting. Methods: We conducted a multi-centre retrospective review of patients treated with T-FP in the first-line setting between October 2014 and October 2022 at two large tertiary referral oncology centres in the United Kingdom. Baseline demographic factors and clinical data were collected and compared between responders and non-responders to re-challenge. PFS and OS were estimated using the Kaplan-Meier method. Results: Data was collected for 225 patients in total treated with first-line trastuzumab. We identified 20 patients who had received a re-challenge with FP-T. Best response to first-line treatment was partial response (PR) for 19/20 patients with 1/20 patients with stable disease (SD). There were no differences between baseline demographic factors or tumour pathological features between patients receiving a re-challenge and those treated with chemotherapy alone. The median platinum free interval was 17.8 months. For the re-challenge disease control rate was 75% with an overall response rate of 25% (7 PR, 0 CR). The median number of subsequent trastuzumab cycles was 7, with a median PFS of 6.1 months and median OS of 10 months. Multivariate Cox-regression analysis identified no factors predictive of response in the re-challenge setting. Conclusions: Re-challenge with trastuzumab plus FP chemotherapy is a possible option for patients with relapse. Larger studies will be required to identify predictive biomarkers to identify those patients most likely to benefit. The role of re-assessment of HER2 status at relapse in those receiving re-challenges requires prospective analysis. Research Sponsor: None.

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Phase II study of GEN-001 in combination with avelumab in patients with PD-L1-positive locally advanced, or metastatic gastric cancer (GC) or gastroesophageal junction cancer (GEJC) who have progressed after second-line (2L) and beyond (GEN001-201 study). First Author: Jieyun Lee, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: The relationship between gut microbiota and the response to immune checkpoint inhibitors is likely due to cross-reactivity between microbial and tumor antigens, enhancing dendritic cell (DC) activation, antigen presentation, and inflammatory cytokine production. GEN-001 is a live biotherapeutic product (LBP) consisting of a lyophilized formulation of a strain of Lactococcus lactis. This study is designed to investigate the safety and efficacy of GEN-001 in combination with avelumab (the PD-L1 inhibitor) for patients with PD-L1 positive advanced GC/GEJC. Methods: This is an open-label, single arm, phase II clinical trial for PD-L1 positive (CPS ≥ 1%) patients with unresectable, locally advanced, or metastatic GC/GEJC who have progressed after second-line and beyond. All patients were treated with GEN-001 (9x10ⁱ¹ CFU, administered as oral once daily) in combination with avelumab (800 mg, administered as an intravenous infusion every two weeks) until progressive disease, unacceptable toxicity, death, or withdrawal. Tumor response was assessed every 8 weeks for 6 months and every 12 weeks thereafter. The primary endpoint was objective response (OR); secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety. Results: As of August 31, 2023, a total of 42 patients were enrolled. 37 patients have been assessed for response. The confirmed partial response (PR) and unconfirmed PR were achieved by 5 patients and 1 patient respectively, 8 patients have experienced as stable disease (SD). Median PFS and median OS were 1.73 months (95% confidence interval [CI], 1.67-2.37 months) and 7.9 months (95% [CI], 6.07-NE months). Treatment-related adverse events (TRAEs) of any grade occurred in 12 patients (28.6%) and Grade ≥ 3 TRAEs occurred in 2 patients (4.8%) out of 42 patients. Conclusions: Treatment of patients with GC/GEJC with GEN-001 in combination with avelumab in the ≤ 3L setting showed promising antitumor activities with an overall manageable adverse event profile. The results from this trial will be updated about its effects on clinical outcome, including survival, safety, and biomarker findings. Clinical trial information: NCT05419362. Research Sponsor: None.

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Short-term outcomes of pedicled jejunum reconstruction after esophagectomy for esophageal cancer. First Author: Mamoru Matano, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Background: The number of patients with esophageal cancer after gastrectomy and patients accompanied with simultaneous gastric cancer has gradually increased because of the prevalence of gastric cancer in Japan. Pedicled jejunum is one of the choices for esophageal reconstruction when the stomach is not available. However, surgical outcomes of jejunal reconstruction and the effect of the timing of gastroscopy remain to be elucidated. Methods: This study was a retrospective, cohort study that included 24 patients who underwent supercharged pedicled jejunal conduit for esophageal reconstruction that was performed in our institution between May 2007 and May 2022. The patients were divided into two groups: gastroscopy was performed before esophagectomy (A group) and gastroscopy was performed simultaneously for accompanied gastric cancer (S group). Surgical outcomes and postoperative complications were compared between the two groups. As a nutritional assessment, perioperative change in body composition such as visceral fat area (VFA) with computed tomography was analyzed. Results: In 24 patients, the median operative time was 769 minutes and the median blood loss was 543 g. Severe postoperative complications developed in 6 cases (25%). The A group included 15 cases and the S group did 9 cases. There was no statistical difference in postoperative complication between the two groups, however, postoperative hospital stay was statistically longer in the S group than in that of the A group (37 days vs. 21 days, p=0.02). Although weight loss at 1 year after operation was almost identical in the two groups, the loss of VFA was more severe in the S group than in the A group (23 % of preoperative VFA vs. 77% of preoperative VFA, p=0.03). Conclusions: The use of a pedicled jejunal conduit after esophagectomy could be performed safely. Postoperative nutritional support is needed for patients especially those who underwent simultaneous gastrectomy. Research Sponsor: None.
Safety and efficacy of zolbetuximab for CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis of randomized controlled trials. First Author: Dai Davi Conquesal Codo, Federal University of Vioça, Vioça, Brazil

Background: Monoclonal antibody (Nivolumab, Trastuzumab, Bevacizumab) with chemotherapy has shown benefit for patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. Zolbetuximab, a new monoclonal antibody against Claudin (CLDN) 18.2 has demonstrated interesting results in clinical trials, however, there is still a need to find a safe and effective first-line treatment, especially for epidermal growth factor receptor (HER2) negative patients. Therefore, we aimed to perform a meta-analysis exploring the use of combined immunotherapy (Zolbetuximab) and standard chemotherapy versus chemotherapy alone. Methods: We searched PubMed, Embase and Cochrane Central for randomized controlled trials (RCTs) comparing Zolbetuximab to chemotherapy alone in patients with CLDN18.2-positive gastric or GEJ adenocarcinoma. The outcomes evaluated were overall survival (OS), Progression Free Survival (PFS), Objective Response Rate (ORR) and Treatment-Emergent Adverse Events (TEAE). Pooled hazard ratio (HR) for PFS and OS endpoints and risk ratio (RR) for ORR and TEAE, with 95% confidence intervals (CI). Statistical analyses were performed using R software version 4.3.1 with a random-effects model. I² analysis was used to assess heterogeneity. Results: Sixty-six studies, three included, with a total of 1340 patients. 671 (49.7%) were part of the intervention group, 769 (57.0%) were male, 360 (27.6%) underwent prior gastrectomy and 1304 (96.7%) had a more than 70% CLDN18.2 cellular staining rate. Age range was 21–83 years. Zolbetuximab was associated with significantly higher PFS (HR = 0.64; CI 0.49–0.84; p = 0.0011; I² = 59.6%) and OS (HR 0.70; CI 0.59–0.84; p<0.0001; I² = 40.0%). TEAE grade ≥ 3 (RR 1.09; CI 1.03–1.16; p = 0.0051; I² = 0.0%) were greater for the intervention group. ORR and serious TEAE had no difference when compared with the control group. Most frequent AEs were nausea (34.6%), vomiting (30.2%) and decreased appetite (18.6%). Conclusions: In summary, the use of Zolbetuximab alongside standard chemotherapy reduces mortality and disease progression, although it might increase the risk for grade ≥ 3 treatment-emergent AEs. Research Sponsor: None.

Management of nausea and vomiting (N/V) following first-line (1L) zolbetuximab + chemotherapy treatment in claudin-18.2 (CLDN18.2)+, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Analysis from the phase 3 SPOTLIGHT and GLOW studies. First Authors: Kohei Shitara, Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: The phase 3 SPOTLIGHT (NCT03540937) and GLOW (NCT03635507) studies showed clinically meaningful, statistically significant improvement in PFS and OS using 1L zolbetuximab + chemotherapy vs placebo (PBO) + chemotherapy in patients (pts) with mG/GEJ. LA - unresectable or mG/GEJ adenocarcinoma. N/V were the most common treatment-emergent adverse events (TEAEs) reported in the zolbetuximab arm of these studies. We report an analysis of the incidence and management of N/V in PFS cohort in SPOTLIGHT and GLOW. Methods: Pts were randomized 1:1 to zolbetuximab + PBO + mFOLFOX6 vs PBO + mFOLFOX6. In SPOTLIGHT (N = 507) were randomized 1:1:1 to zolbetuximab + CAPOX vs PBO + CAPOX. In both studies, neurokinin-1 receptor blockers (NK-1), selective serotonin receptor blockers (5-HT3), and other prophylactic antiemetic regimens were recommended to prevent and mitigate N/V per institutional care and guidelines. Results: A total of 279 pts in SPOTLIGHT and 253 pts in GLOW received zolbetuximab + chemotherapy. In SPOTLIGHT and GLOW combined, nausea occurred in 56% vs 16% of pts, and vomiting occurred in 43% vs 15% of pts in the first vs second zolbetuximab infusions, respectively, lower incidences of N/V were observed thereafter. During the first zolbetuximab infusion, the first episode of N/V occurred within 1 hour (median time, 48 min in SPOTLIGHT and 56.5 min in GLOW). Antiemetic usage and associated N/V rates are presented in the Table. The 96 pts in SPOTLIGHT and 51 pts in GLOW who had infusion modications in cycle 1 due to TEAEa had numerically higher infusion rates than pts without infusion modifications; 85% of these modifications in SPOTLIGHT and 79% in GLOW were due to N/V. Zolbetuximab was discontinued in the first 9 weeks in 11 and 7 pts in SPOTLIGHT and 6 and 4 pts in GLOW due to nausea or vomiting, respectively. Conclusions: In SPOTLIGHT and GLOW, slower infusion rate and use of antiemetic modications may help to mitigate N/V in pts. These strategies will be important to support continued treatment. Treatment with zolbetuximab has clinical benefit with zolbetuximab + chemotherapy. Clinical trial information: NCT03540937 and NCT03635507. Research Sponsor: Astellas Pharma Inc.

Camrelizumab combined with concurrent chemoradiotherapy for locally recurrent esophageal cancer. A single-arm, open-label study. First Author: Anwar Saeed, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Camrelizumab (M308500) is a humanized IgG1 monoclonal antibody that targets programmed death-ligand 1 (PD-L1), and other prophylactic antiemetic regimens were recommended to prevent and mitigate N/V. Methods: Patiwns received camrelizumab (200 mg q2w, continuous medication until disease progression, intolerable toxicity, or withdrawal). Antiemetic usage and associated N/V rates are presented in the Table. In summary, the use of Zolbetuximab alongside standard chemotherapy reduces mortality and disease progression, although it might increase the risk for grade ≥ 3 treatment-emergent AEs. Conclusions: In summary, the use of Zolbetuximab alongside standard chemotherapy reduces mortality and disease progression, although it might increase the risk for grade ≥ 3 treatment-emergent AEs. Camrelizumab combined with concurrent chemoradiotherapy for locally recurrent esophageal cancer. A single-arm, open-label study. First Author: Anwar Saeed, University of Pittsburgh Medical Center, Pittsburgh, PA

Phase II trial of cabozantinib ( cabo) plus durvalumab (durva) in chemotherapy refractory microsatellite stable (MSS) patients with advanced gastric and esophageal (G/E) adenocarcinoma: CAMILLA G/E cohort results. First Author: Luoyang, China

Background: A total of 279 pts in SPOTLIGHT and 253 pts in GLOW received zolbetuximab + chemotherapy. In SPOTLIGHT and GLOW combined, nausea occurred in 56% vs 16% of pts, and vomiting occurred in 43% vs 15% of pts in the first vs second zolbetuximab infusions, respectively, lower incidences of N/V were observed thereafter. During the first zolbetuximab infusion, the first episode of N/V occurred within 1 hour (median time, 48 min in SPOTLIGHT and 56.5 min in GLOW). Antiemetic usage and associated N/V rates are presented in the Table. The 96 pts in SPOTLIGHT and 51 pts in GLOW who had infusion modifications in cycle 1 due to TEAEa had numerically higher infusion rates than pts without infusion modifications; 85% of these modifications in SPOTLIGHT and 79% in GLOW were due to N/V. Zolbetuximab was discontinued in the first 9 weeks in 11 and 7 pts in SPOTLIGHT and 6 and 4 pts in GLOW due to nausea or vomiting, respectively. Conclusions: In SPOTLIGHT and GLOW, slower infusion rate and use of antiemetic modifications may help to mitigate N/V in pts. These strategies will be important to support continued treatment. Treatment with zolbetuximab has clinical benefit with zolbetuximab + chemotherapy. Clinical trial information: NCT03540937 and NCT03635507. Research Sponsor: Astellas Pharma Inc.
Efficacy and safety of dendrimer-enhanced (DEP) cabazitaxel (CTX-SPL9111) in advanced esophagogastric cancers in a phase 1/2 trial. First Author: Hyunju Shin, Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: There is a significant unmet need in esophagogastric cancers (EGC) due to limited effective treatments (Tx) and poor prognosis. Dendrimers are highly branched nanoparticles that enable sustained delivery of cytotoxic drugs and achieve selective tumor targeting via an enhanced permeability and retention effect. DEP cabazitaxel is a highly optimized dendrimer formulation of cabazitaxel. Unlike standard cabazitaxel, DEP cabazitaxel does not contain surfactants associated with anaphylaxis, and avoids the need for steroid/anasthetic pre-medication. The objective of this Phase 1/2 trial was to assess preliminary efficacy and safety of DEP cabazitaxel in patients (pts) with advanced solid tumors including EGC, for which standard cabazitaxel is not approved.

Methods: In the P2 part of the trial, advanced EGC pts with measurable disease were treated with DEP cabazitaxel 20 mg/m² cabazitaxel, the recommended Phase 2 dose, IV 3-weekly. Anti-tumor activity was assessed by RECIST v1.1, safety by CTCAE v4.03. (EudraCT 2017-003424-76). Results: Fifteen pts with advanced EGC were enrolled; 9 adenocarcinoma (ADENCA) (3 gastric, 2 esophageal and 4 EG junction) and 6 esophageal squamous cell carcinoma (ESCC); median age 62 yrs (26-73 yrs), with all pts having ≥3 prior anticancer Tx, and the majority (9) having progressed on or immediately after 1 line Tx (11). All had ≥1 platinum-based regimen and 4 pts had received prior taxanes. Pts received a median of 4.5 DEP cabazitaxel cycles without the need for routine steroid/anasthetic or primary G-CSF prophylaxis. In all evaluable pts, disease control rate (DCR) was 80%. Disease control was observed in both histological subtypes and was durable, including stable disease (SD) for up to 27 weeks and partial responses (PR) for up to 17 weeks, with objective response rate (ORR) of 30%. In EG ADENCA pts, DCR was 100%, ORR was 33%, and median progression free survival (mPFS) was 4.0 months. In ESCC pts, DCR was 50% and ORR was 25%, with mPFS of 1.9 months. DEP cabazitaxel was well-tolerated with mostly mild (62.9%, Grade (G) 1/2/3 20.2%, G2/3) treatment-related adverse events (TRAEs), including nausea, vomiting, fatigue, neuropathy, neutropenia (only 1 pt had G-CSF Tx, 1 pt had secondary G-CSF prophylaxis) and anemia, that were like those observed with standard cabazitaxel Tx. Of seven TRAEs (G1/2/3) (9%) most (86%) were observed in 2 pts, including neutropenia, anemia, thrombocytopenia, fistula, elevated liver enzymes.

Conclusions: DEP cabazitaxel exhibited highly encouraging anti-tumor activity in ≥1L advanced EGC in multiple anatomic locations and of different histological sub-types. The preliminary efficacy and safety results compare favorably to available treatment options, and highlight the promising clinical potential of DEP cabazitaxel in advanced EGC. Clinical trial information: EudraCT 2017-003424-76. Research Sponsor: Starpharma Pty Ltd.

Pembrolizumab, radiotherapy, and chemotherapy in neoadjuvant treatment of malignant esophagogastric diseases (PROCED): Assessment of survival and patterns of recurrence in a prospective, phase 2 single-arm trial. First Author: Pooja Karulkonda, Duke Cancer Institute, Durham, NC

Background: Locally advanced esophagogastric adenocarcinoma (EGA) is commonly treated with neoadjuvant chemoradiation (CRT) prior to surgical resection. Adjuvant immunotherapy has been shown to improve outcomes for these patients. The primary objective of this trial was to investigate whether neoadjuvant pembrolizumab (P) + CRT improves pathologic complete response (pCR) compared to historical control of neoadjuvant CRT alone. Exploratory endpoints included time to local recurrence (TTLR), time to distant recurrence (TDDR), progression-free survival (PFS), and overall survival (OS).

Methods: Single-institution, prospective phase II trial (NCT03064490) evaluating neoadjuvant P + CRT followed by adjuvant P in patients with locally advanced operable EGA. CRT (45 Gy in 25 fractions with concurrent, weekly carboplatin [AUC 2] and paclitaxel [50mg/m² of BSA]) with three cycles of P were administered as neoadjuvant therapy. Patients also received three cycles of adjuvant P. Pathologic response was scored from 0-3 based on tumor regression grading (TRG): 0 indicating a complete response, 1 marked response (~10% residual disease), 2 partial response, and 3 or no response. pCR was defined as the absence of viable tumor cells at the primary tumor site and all resected lymph nodes in the surgical specimens (ypT0N0, TRG 0). Major pathologic response (MPR) was defined as TRG 0-1. Treatment-responders (RT) are those with MPR, while non-responders (NR) are those with TRG ≥2. TTLR was time from enrollment to local recurrence (LR); distant recurrences (DR) were defined and were not included. Treatment duration (TTDR) was time from enrolment to death due to any cause. OS was time from enrolment to death due to any cause. The Kaplan-Meier method was used to estimate TTLR, TTDR, PFS, and OS. Two-sided statistical tests were performed with an α of 0.05 considered significant.

Results: 35 patients were enrolled from 2017-2022. 30 underwent neoadjuvant P + CRT followed by surgical resection. pCR and MPR rates were previously reported: 35.5% and 50%, respectively. Median follow-up of the whole cohort was 35.5 mo. PFS was significantly improved in R vs NR (p=0.046), and there was a trend towards improved OS (p=0.084), and TTDR (p=0.069). 11 TRGR pts had no significant difference in TTLR (p=0.126). At three years, in R vs NR, PFS was 77.2% vs 46.2%, OS was 80.0% vs 58.3%, TTLR was 100% vs 81.8%, and TDDR was 81.8% vs 53.8%. Conclusions: Patients undergoing neoadjuvant P + CRT for EGA experienced higher rates of pCR/MPR compared to historical controls treated with CRT alone. MPR correlated with improved PFS, with a trend towards improved OS, indicating the clinical significance of pathologic response. These correlations appear to be driven primarily by decreased risk of developing distant metastases. Clinical trial information: NCT03064490. Research Sponsor: Merck.
The role of exosomal LINC00853 in gastric cancer progression. First Author: Sang Kil Lee, Yonsei University College of Medicine, Seoul, South Korea

Background: Examination of various substances contained in exosomes (EXOs) as biomarkers is being actively conducted. Long non-coding RNAs (lncRNAs) are garnering interest in the diagnosis of gastric cancer. In this experiment, we attempted to obtain IncRNAs that drive the onset and recurrence of gastric cancer and elucidate the mechanism to observe their potential as exosomal biomarkers. Methods: IncRNA expression profiling was conducted using ArrayStar Human LncRNA array 2.0 for the patient’s tissues who underwent endoscopic resection that reflected early gastric cancer onset and recurrence. The proliferation, apoptosis, invasion, and migration of AGS and MKN74 cells were measured after treatment with pcDNA over expressing vector and two different siRNAs. To observe the interaction between IncRNA and MAP17, RNA immunoprecipitation (IP) and electrophoretic mobility shift assay were conducted. EXOs were extracted from patient samples and gastric cancer cell lines, which were then administered to gastric cancer cells. Results: Five target IncRNAs (LINC00853, LINC00634, LINC01535, GAPLINC, and AC017002.1) were selected by performing a IncRNA microarray analysis. The validation results showed that LINC00853 was upregulated in gastric cancer tissues compared to that in paired adjacent non-cancer tissues. LINC00853 induced proliferation and suppressed apoptotic signaling of AGS and MKN74 cells. LINC00853 promoted the invasion and migration of AGS and MKN74 cells. LINC00853 bound with its neighbor gene MAP-17 and activated it via the downstream PDZK1/AKT signaling pathway. LINC00853 and MAP-17 cooperatively acted as oncogenes in gastric cancer. EXOs derived from patients with gastric cancer and those from gastric cancer cell lines (AGS, MKN74) contained LINC00853. Knockdown of LINC00853 decreased LINC00853 expression in EXOs, which, in turn, reduced the oncogenicity of LINC00853 exosome in AGS cells. Cellular and exosomal LINC00853 exert an oncogenic effect via MAP-17-related cell signaling in gastric cancer. Conclusions: Exosomal LINC00853 can be a candidate biomarker of occurrence of recurrence of gastric cancer. Research Sponsor: None.

Predicative role of homologous recombination deficiency (HRD) for irinotecan in combination with venadaparib, a novel PARP1/2 inhibitor, as third-or four-line treatment in patients with advanced gastric cancer. First Author: Do-Youn Oh, Medical Oncology, Seoul National University Hospital, Seoul, South Korea

Background: Tumors with homologous recombination deficiency (HRD), including BRCA and ATM mutations, have shown to predict response to poly(ADP-ribose) polymerase (PARP) inhibitors. The associations between treatment efficiency of PARP inhibitor-based regimen and mutations in BRCA (BRCA2) or ATM gene (ATM) are not well known in previously treated advanced gastric cancer (GC). Combining PARP inhibitor and irinotecan is known to synergize cytotoxicity. The aim of this analysis was to evaluate the association between HRD and efficacy of irinotecan and venadaparib combined, in patients with metastatic GC who had failed at least 2 lines of therapy. Methods: MTT assays were performed in vitro to verify and characterize synergism between venadaparib and SN-38. Data were analyzed using the GraphPad Prism (version 5.5.1) and Compusyn (version 1.0) software. Patients with at least two prior palliative treatments were enrolled in a randomized design. Clinical trial information: NCT04725994. Research Sponsor: None.

Dysbiosis in gastric mucosal microbiota associated with gastric carcinogenesis. First Author: Byung-ook Kim, The Catholic University of Korea, Incheon, South Korea

Background: Gastric microbiota, including H. pylori, may play a role in the development of gastric cancer. This study aimed to investigate the gastric microbiota throughout the stages of gastric carcinogenesis, encompassing atrophic gastritis, gastric dysplasia, and gastric adenocarcinoma. Methods: From December 2021 to August 2023, we collected gastric mucosal tissue samples from patients with atrophic gastritis, gastric dysplasia, and early gastric cancer. Subsequently, we conducted 16S rRNA gene profiling through next-generation sequencing. We compared alpha-diversity and beta-diversity within each group and analyzed the taxonomic composition. Notably, H. pylori high-grade dysplasia, and early gastric cancer. The 16S rRNA gene profiling through next-generation sequencing. We compared alpha-diversity and beta-diversity within each group and analyzed the taxonomic composition. Results: This study included a total of 98 patients, comprising 16 with atrophic gastritis, 23 with low-grade dysplasia, 15 with high-grade dysplasia, and 44 with early gastric cancer. The H. pylori infection status was comparable across all groups. While there was a difference in alpha diversity between tumor lesions and normal stomach lesions, it did not reach statistical significance. Notably, Phyllobacterium was dominant in early gastric cancer, Prevotella in high-grade dysplasia, and Kocuria in low-grade dysplasia. Furthermore, within the early gastric cancer group, Bacillus was widely distributed in cases of differentiated type adenocarcinoma. Conclusions: The analysis of microbiota collected from Korean stomach tissue revealed distinct microbial distributions across the various stages of gastric carcinogenesis. Research Sponsor: None.
Detection of early-stage gastrointestinal cancers by micronuclei DNA from erythrocytes. First Author: Haobo Sun, School of Life Sciences, Westlake University; Institute of Basic Medical Sciences, Westlake Institute for Advanced Study, Hangzhou, China

**Background:** Gastrointestinal (GI) cancers account for over a third of cancer deaths. However, their early detection remains a challenge. Micronuclei (MN) are extranuclear bodies containing damaged chromosome segments indicative of genomic instability. Increased MN frequency in hematopoietic cells is observed in patients with solid tumors. We have developed a method (W02021/228246 A1) for purifying and characterizing micronuclei DNA (mMDNA) in erythrocytes from peripheral blood. Here, we evaluated the potential of mMDNA for early-stage GI cancer detection, including colorectal (CC) and gastric (GC) cancers. **Methods:** Peripheral blood (1 ml) was collected from healthy donors (HD) and cancer patients mMDNA isolation and purification from erythrocytes. Participants were randomly divided into training, validation and independent test cohorts in a 7:2:1 ratio, maintaining similar cancer types, CC/GC/HD ratio, gender and age distribution. Distinct mMDNA features between cancer patients and HDs were identified using sequencing data. Logistic regression algorithms were applied using these features for cancer detection. **Results:** The study enrolled 1046 participants, including 419 HDs, 366 CC and 261 GC cases. Of these, over half were diagnosed with early-stage diseases; TNM stage I accounted for 38.7%, stage II for 22.8%, stage III for 30.5% and stage IV for 8.0%. The cancer detection model with mMDNA features yielded an overall accuracy of 84.8%, with a sensitivity of 84.1% and specificity of 85.7%. For individual cancer types, sensitivity was 89.2% for CC and 76.9% for GC. For early-stage (stage I-II) CC and GC, the model demonstrated sensitivities of 88.9% and 76.5%, respectively, at 85.7% specificity. **Conclusions:** Unlike cell-free DNA, mMDNA are chromosomal fragments in the cytoplasm. The abundance of erythrocytes in peripheral blood provides an easily accessible source for mMDNA enrichment. This pilot study illustrates the potential of mMDNA as a tool for early GI cancer detection, contributing to large-scale efforts towards developing an effective GI cancer screening test. **Research Sponsor:** Timing Biotech.

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Exploratory analysis of biomarkers of response to durvalumab in advanced HER2-negative oesophago-gastric adenocarcinoma within a phase 2 clinical trial. First Author: Hazel Lote, The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom

**Background:** Advanced oesophago-gastric cancers have showcased varied responses to immunotherapy based on biomarkers such as tumour mutation burden (TMB), genomic instability, and PD-L1 expression. However, these markers may not fully capture tumour immunotherapy based on biomarkers such as tumour mutation burden (TMB), genomic instability, and PD-L1 expression. However, these markers may not fully capture tumour immunotherapy response. A pilot substudy on a selected cohort (n=24) of these patients was designed to explore the potential of immunogenomics evolutionary-based metrics, notably dN/dS, as a tool for early GI cancer detection, contributing to large-scale efforts towards developing an effective GI cancer screening test. **Research Sponsor:** Timing Biotech.

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The expanded indications of HER2-targeted therapies by monitoring of circulating tumor cells. First Author: Yasuaki Kimura, Saitama Medical Center, Jichi Medical University, Saitama, Japan

**Background:** Despite success in the HER2 targeted therapies for metastatic gastric cancer patients, the conventional assessment of HER2 status in tumor tissue specimens is still imperfect. Twenty-seven patients with metastatic gastric cancer were treated according to histological HER2 status. On-chip sorting system was used for the isolation of circulating tumor cells (CTCs) before treatments. Epithelial mesenchymal transition (EMT) was assessed by the vimentin and cytokeratin. DNA was extracted from CTCs and applied to the gene panel with 409 cancer related genes. The fluorescence signal intensity >= 50 is set to be a threshold value for distinguishing between positive and negative HER2 on CTCs. **Results:** Thirty patients (48%) with HER2 positive in tumor tissues (Group A) were treated with cytotoxic agents and trastuzumab (anti HER2 antibody) while 14 patients (52%) were negative and treated with cytotoxic agents. In these 14 patients, 8 patients (50%) showed HER2 positive (Group B) and 6 patients (22%) displayed HER2 negative (Group C) on CTCs. Increased expression of EMT was seen in Group A and B, indicating they are likely to have metastasis. Group B showed worse PFS than others (13.8 M in A, 7.0 M in B and not reached in C, p=0.012), suggesting Group B could be a candidate for expand indication of Trastuzumab. Genomic analysis showed some mutated genes involved in the PI3K signaling pathway which associated with drug resistance. **Conclusions:** Monitoring of circulating tumor cells leads to the expand indication of the HER2 targeted therapies in patients with metastatic gastric cancer. **Research Sponsor:** None.

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Effect of sitravatinib combined with PD-1 blockade on cytotoxic T-cell infiltration by M2 to M1 tumor macrophage repolarization in esophageal adenocarcinoma. First Author: Aishten Omstead, Allegheny Health Network Cancer Institute, Allegheny Health Network, Pittsburgh, PA

**Background:** Esophageal adenocarcinoma (EAC) is a deadly cancer with a low survival rate and limited treatment options. Receptor tyrosine kinase inhibitor, sitravatinib, selectively targets tumor associated macrophage (TAM) family receptors, AXL, TYRO3 and MERTK, and split family receptors, VESFR, PDRFR1, KIT and MET. In solid tumors, sitravatinib has been shown to potentiate PD-1 blockade by production of pro-inflammatory cytokines and re-locating MDSCs, Tregs and TAMs, in the tumor microenvironment (TME). **Methods:** End-to-side esophageojunostomy was performed on a cohort of 96 rats to induce gastrointestinal esophageal reflux, leading to EAC carcinogenesis. At 32 weeks post-operative, all surviving animals underwent endoscopic examination with biopsy and a pre-treatment MRI. All tumor bearing animals were randomized to a dose of 10mg/kg of sitravatinib (S) or vehicle control (VC) for three cycles, and PD-1 inhibitor, AUNP-12 (IO), was administered on day 12 of each 14 day cycle, at a dose of 3mg/kg. At 38 weeks post-operative, animals received a post-treatment MRI and were euthanized. Safety and efficacy were evaluated by on-treatment mortality, pre- and post-treatment MRI, immunohistochemistry, immunofluorescence and real-time PCR. **Results:** The S+/IO groups demonstrated a higher on-treatment mortality when compared to the VC+/IO groups (p<0.001). Pre-to post-treatment, mean MRI tumor volume decreased by 32% and 73% in the S-D and S+IO animals and increased by 98% and 160% in the VC+D and VC+IO animals, respectively (p<0.001). Increased apoptosis and decreased proliferation were confirmed through Cas-3 and Ki-67 immunohistochemistry, respectively, in both S treatment groups (p<0.001). CD8+ T-cell infiltration was upregulated, and M2 to M1 macrophage phenotype repolarization was demonstrated in all treatment groups by immunofluorescence (p<0.01). Downstream gene expression demonstrated upregulation of pro-inflammatory cytokines including TNF-α, IFN-γ, IL-5, IL-6, IL-12 and downregulation of anti-inflammatory cytokines including TGF-β, IL-4, IL-10, and IL-13 in S treatment groups compared to VC treatment groups (p<0.05). There was no significant difference in pre-treatment PD-L1 levels between any of the treatment groups (p>0.05). Pre- to post-treatment qRT-PCR demonstrated significant inhibition of pathway genes AXL, AKT, MERTK and PI3K in the treatment animals (p<0.001). Additionally, pre-treatment AXL and PD-L1 levels were significantly higher in major responders (>80% tumor reduction) when compared to the non-responders (<25% tumor reduction or progression), in the combined S+/IO groups (p<0.05). **Conclusions:** This study establishes a favorable combinatorial strategy using sitravatinib to overcome immunosuppression in the TME, providing strong rationale for future clinical strategies in the treatment of EAC. **Research Sponsor:** Crowley-Carter Foundation; Baylor Scott & White Dallas Foundation.

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Relationship between the number of positive MSI markers and the efficacy of NIVO+IPI therapy in MSI-H gastric cancer: A subgroup analysis of NO LIMIT study (WJOG13320G/CA209-7W7). First Author: Kenzo Hirata, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Background: Although high instability of microsatellite lesion (MSI-H) is an established biomarker for response to immune checkpoint inhibitors, the relationship between the number of MSI markers and the efficacy of immune checkpoint inhibitors in MSI-H tumors has not been well elucidated. NO LIMIT (WJOG13320G/CA209-7W7) is a phase II trial of nivolumab plus low-dose ipilimumab (NIVO+IPI) for MSI-H advanced gastric or esophageogastric junction cancer (GC) in the first-line setting. Here, we investigated the relationship between the number of positive MSI markers and the efficacy of NIVO+IPI in NO LIMIT study. Methods: Eligible patients were unresectable advanced, recurrent, or metastatic GC with confirmed as MSI-H with the MSI-IVD Kit (FALCO), where two or more of the five MSI markers are defined as positive. Nivolubam (240 mg) biweekly and ipilimumab (1 mg/kg) every six weeks were given until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR) assessed by a blinded independent central review. Secondary endpoints included progression-free survival (PFS), overall survival (OS), safety, and the association between number of positive MSI markers and clinical efficacy (ORR, PFS, OS). The analysis was performed 18 weeks after the first dose in the last patient, with a median follow-up of 9 months (range, 4.0-18.0). Results: The breakdown of MSI markers in the 29 patients enrolled in NO LIMIT was as follows: BAT-26 (26/26, 100%), NR-21 (25/29, 86.2%), BAT-25 (25/29, 86.2%), MONO-27 (29/29, 100%), NR-24 (27/29, 89.4%). Since most of the cases were positive for all five of them (the number of cases with 2, 3, 4, and 5 positive markers was 2, 2, 1, and 24, respectively), we dichotomized the last patient, with a median follow-up of 9 months (range, 4.0-18.0).

Proportion and distribution of PD-L1 expression and associated clinicopathologic features in patients with microsatellite instability-high gastric cancer: A subgroup analysis of NO LIMIT study. First Author: Sun Mi Lee, Indiana University School of Medicine, Indianapolis, IN

Background: The frequency of microsatellite instability-high (MSI-H) phenotype in sporadic gastric cancers (GCs) widely varies from 8% to 20%. From prior data, MSI-H phenotypes are significantly associated with female sex, older age, antral location of the tumor, well to moderate differentiation, intestinal type, non-signet ring cell component, mucinous histologic type, a moderate to severe lymphoid stromal reaction, and a lower TNM stage. This study investigated the proportion and distribution of PD-L1 expression of MSI-H GCs compared to microsatellite stable (MSS) GCs. Results: Of 847 cases of unselected GC, MSI analysis was performed on all GC cases by immunohistochemistry for mismatch repair proteins followed by multiplex polymerase chain reaction. Among them, 72 GCs were found to be an MSI-H phenotype. After matching the T category of GCs, 200 cases of GC with MSI phenotype were selected for a control group. Immunohistochemistry for PD-L1 (SP263) was performed on 72 MSI-H GCs and 200 MSS GCs. Results: Patients with MSI-GC were significantly associated with advanced age (p < 0.001), advanced tumor (p = 0.0173), antral location of the tumor (p = 0.0018), and T2 and T3 category (p = 0.0031) but not T1 or T4 category. Histologically, MSI-H GCs occurred frequently in ulcerofungating mass (45.8%, p < 0.0001), intestinal type (73.6%, p < 0.0012), well to moderately differentiated tumor (56.9%, p = 0.0102), tubular histologic type (66.7%, p = 0.0013), tumor necrosis (18.1%, p < 0.0001), and peritumoral neutrophilic infiltrate (40.3%, p < 0.0011) compared to those of 200 MSS GCs. In the evaluation of PD-L1, 55 (76.4%) MSI-H tumors revealed PD-L1 expression with ≥ 1 CPS. The predominant PD-L1 staining was found in intratumoral and peritumoral immune cells (66.7%) than within tumor cells (9.7%). The distribution of positive immune cells was predominantly located in the periphery of the tumor (37.5%) than within the tumor (9.7%). According to the criteria for PD-L1 positivity as at least 10 CPS, approximately 50% of MSI-H GCs were considered PD-L1 positive tumors with at least 10 CPS. Conclusions: In this study, the prevalence of MSI-H phenotype is approximately 6.5% of unselected GCs. Approximately 76% of patients with MSI-H tumors showed PD-L1 expression with at least 1 CPS, and 50% revealed PD-L1 expression with at least 10 CPS, who can respond better to immune checkpoint inhibitors with promising therapeutic benefits. Due to the peritumoral expression of immune cells in PD-L1 positive GCs with MSI-H phenotype, different endoscopic approaches to obtain tumor tissues for PD-L1 evaluation would be considered, such as sampling tissues at the tumor periphery.

Conclusions: The prevalence of MSI-H in localized GC is significantly higher than metastatic GC (11.26% vs. 3.30%, p < 0.001). A higher proportion showed PD-L1 expression (73.91%) in MSI-H than in MSS tumors, suggesting that MSI-H status is associated with PD-L1 (p < 0.05). These results provide a basis for identifying GC patients who may benefit from anti-PD-1/PD-L1 therapy. Research Sponsor: None.

Correlation MSI with expression PD-L1 (CPS).

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Oncogenic aberrations in primary gastric cancer tumors to predict metachronous peritoneal metastasis.

First Author: Joseph J Zhao, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore

Background: Peritoneal metastases (PM) in gastric cancer (GC) portend a poor prognosis. Yet, there are a paucity of data on underlying genomic alterations predictive of PM.

Methods: Two-hundred and nine patients who underwent primary tumor (PT) surgical resection were included in the prospective cohort. Whole exome sequencing (WES) of these resected PT GC specimens (average coverage 129X for tumor samples, 70X coverage for matched normal/blood controls) were undertaken. Participants were followed-up longitudinally for peritoneal metastases.

Results: Fifty-one (51/209, 24.4%) patients developed nine patients to underwent primary tumor (PT) surgical resection were included in the prospective cohort.

Concordance among three programmed death-ligand 1 (PD-L1) scoring methods and their association with clinical outcomes of tisitemunab (TIS) monotherapy in esophagosophagus squamous cell carcinoma (ESCC).

First Author: Yongqian Shu, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Multiple scoring methods and cut-offs have been developed to evaluate tumor PD-L1 expression status in patients with ESCC, and PD-L1 expression level has been associated with the degree of response to anti-programmed cell death protein 1 (PD-L1/PD-L1) therapy. Here, we retrospectively investigated concordance between three PD-L1 scoring methods and their association with clinical outcomes in RATIONALE-302, a phase 3 study of the anti-PD-1 antibody TIS vs investigator-chosen chemotherapy (IC) as secondary treatment for advanced unstable/unresectable metastatic ESCC (NCT03438043).

Methods: Patients enrolled in RATIONALE-302 with evaluable PD-L1 expression by the tumor area positivity (TAP) score (based on visual estimation of positive tumor cells [TCs] and tumor-associated immune cells [ICs]) using the VENTANA PD-L1 (SP263) assay were categorized at a 1% cutoff. Stained slides from those patients were rescored post hoc using both combined positive score (CPS) methods, and scoring (based on visual estimation of positive tumor cells [TCs] and tumor-associated immune cells [ICs]) using the VENTANA PD-L1 (SP263) assay were categorized at a 1% cutoff. Stained slides from those patients were rescored post hoc using both combined positive score (CPS) methods.

Results: Of 512 pts enrolled, 364 had evaluable TAP scores (TIS, n=188; IC, n=188), of which 355 had evaluable post-hoc CPS and TC scores (TIS, n=175; IC, n=175). TAP score and CPS showed high concordance in terms of overall percentage agreement (OAA; 90% [95% confidence interval (CI): 86, 93]) and Cohen’s Kappa (0.79 [95% CI, 0.72, 0.85]), while TAP and TC scores had lower concordance (OAA: 78% [95% CI: 73, 82]; Cohen’s Kappa: 0.56 [95% CI: 0.47, 0.64]). OS benefit with TIS vs IC in PD-L1 subgroups defined by TAP, CPS, and TC score cutoffs were generally similar. Complete concordance analysis showed comparable treatment effect by TAP score at 1% cutoff, CPS at cutoff of 10, and TC score at 1% cutoff based on SP263 staining. TAP score and CPS at these cutoffs exhibited substantial concordance. The results indicate that the less time-consuming, visually estimated TAP score and CPS may be interchangeable for clinical measurement of PD-L1 expression in patients with ESCC. Clinical trial information: NCT03438043.

Research Sponsor: Beike Geni, Ltd.
Molecular profiling of hepatoid adenocarcinoma and adenocarcinoma with enteroblastic differentiation. First Author: Youseke Matsumoto, Division of Gastrointestinal Surgery, Shizuoka Cancer Center, Nagasaki, Japan

Background: Hepatoid adenocarcinoma (HAD) and adenocarcinoma with enteroblastic differentiation (ACED) are rare types of gastric cancer that produce alpha-fetoprotein (AFP) and morphologically resemble liver or fetal gut cells. The molecular characteristics of these tumors are poorly understood. We aimed to investigate the molecular profile of HAD and ACED in the comparison with common type of gastric cancer.

Methods: We analyzed tissue and blood samples from 496 patients who underwent gastrectomy for gastric cancer and participated in the Project HOPE (High-tech Omics-based Patient Evaluation) in our hospital, from 2014 to 2019. We excluded patients with other special types of gastric cancer, remnant gastric cancer and preoperative chemotherapy. We analyzed gene mutation, copy number, and gene expression between 10 HAD/ACED and 486 common types of gastric cancers. Results: The mutated genes with high frequency (> 20%) in HAD/ACED were TP53 (100%) CSM03 (30%), LRP1B, FAT3, TG, APOB, CREBBP, PASK, DROSHA and STK40 (20%). The tumor mutation burden (TMB) of all the cases were less than 10. TMB of HAD/ACED was equivalent to that of common type of gastric cancer with microsatellite stable type. The copy number of 20q13.2 encoding SALL4 was significantly gained in HAD/ACED (p = 0.03). Furthermore, 17 genes were highly expressed in these tumors, and many of these genes were associated with hepatocytes and fetal organs, including LIN28B, IGF2BP1, and HMGA2, which are related to TP53 mutation. Conclusions: Our molecular profiling revealed similarities between HAD/ACED and hepatocytes/fetal organs and high expression of LIN28B, IGF2BP1, and HMGA2, which are associated with TP53 inactivation. These results suggest that these genes may define morphological features of HAD/ACED. Research Sponsor: None.

396 Poster Session
Circulating exosomal microRNA signature to predict peritoneal metastasis in patients with advanced gastric cancer. First Author: Yuma Wada, Tokushima University, Tokushima, Japan

Background: Despite of radical operation, about half of gastric cancer (GC) patients with advanced GC develop peritoneal metastasis (PM) and the patients with PM has poor prognosis. However, because staging laparoscopy was a promising approach for advanced disease, the patients, identification of PM by using liquid biopsy can be useful in patients with GC. We developed an integrated exosomal miRNA panel and established a risk-stratification model, which was combined with miRNA panel and currently used tumor markers (CEA, CA19-9, CA125, and CAT2-4 levels). Results: Our comprehensive discovery effort identified a 4-miRNA panel that robustly predicted the metastasis, with an excellent accuracy in TCGA dataset (AUC=0.86). We successfully established a circulating exosomal miRNA panel with remarkable diagnostic accuracy in the clinical training (AUC=0.85) and validation (AUC=0.86) cohorts. Moreover, the predictive accuracy of the panel was significantly superior to conventional clinical factors (P<0.01), and the risk-stratification model was dramatically superior to the panel and currently used clinical factors for predicting PM (AUC=0.94, univariate: OR = 77.80, P < 0.01, multivariate: OR = 57.71, P = 0.01). Conclusions: Our novel risk-stratification model for predicting PM has a potential for clinical translation as a liquid biopsy assay in patients with GC. Our findings highlight the potential clinical impact of our model for improved selection and management of patients with this malignancy. Research Sponsor: None.

397 Poster Session
Role of heat shock protein 90 in hypoxia-induced angiogenesis and epithelial-mesenchymal transition for esophageal squamous cancer cells. First Author: Ching Tzeo, Cardinal Tin Hospital, New Taipei City, Taiwan

Background: Hypoxia is known as an important trigger for the development and progression of human cancers. Heat shock proteins (Hsps) may be up-regulated in response to cellular stressors including hypoxia. To date, the functional role of Hsps within hypoxic tumor microenvironment for esophageal squamous cell cancer (ESCC) remains poorly defined. Methods: CoCl2 was used to induce hypoxia that mimics a hypoxic tumor microenvironment in cultured ESCC cells. Successful induction of hypoxia was confirmed by 2′,7′-dichlorofluorescein diacetate (DCFDA) assay by detection of cellular reactive oxygen species (ROS). 7-Dimethylaminoethylamino-17-deethoxygedelaminycin (17-DMAG), a selective Hsp90 inhibitor, was used to treat 2 ESCC cell lines, KYSE-170 and -510 cells pretreated with or without CoCl2, an agent to induce a hypoxic tumor microenvironment. Cytotoxicity (MTT) and migration assays were conducted in KYSE-17 and -510 ESCC cells in response to different concentrations of CoCl2, followed by protein expression of Hsp 90, vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1a (HIF-1a), mTOR as well as markers related epithelial-mesenchymal transition (EMT) such as E-cadherin, by immunoblot or ELISA. In parallel, cell proliferation and migration assays of ESCC cells were analyzed. Results: CoCl2 induced hypoxia was supported by an induction of reactive oxygen species (ROS). CoCl2 (200 mM) significantly suppressed cell viability and proliferation with a concomitant up-regulation of VEGF and HIF-1a in a dose-dependent fashion. In contrast, cell migration was significantly increased in response to CoCl2, while down-regulating E-cadherin with concomitant increase in Snail expression. 17-DMAG decreased expression of VEGF and HIF-1a. In addition, it inhibited cell migration and invasion of ESCC cells were analyzed. Conclusions: Our data have shown that CoCl2 induced hypoxia promotes EMT and angiogenesis, which are inhibited by 17-DMAG, suggesting that hypoxia induced EMT and angiogenesis is Hsp 90 dependent in ESCC. Research Sponsor: Ministry of Science and Technology, Republic of China.
**Treatment development targeting Hippo pathway for scirrhous type gastric cancer.** First Author: Yuchiro Miki, Department of Gastroenterological Surgery, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

**Background:** Treatment outcome of gastric cancer (GC) has been improved by minimally invasive surgery, and development of new drugs including immune checkpoint inhibitors. However, survival for patients with scirrhous type (SGC, Type4) gastric cancer is dismal. **Methods:** We collected miRNAs form exosomes released from cancer associated fibroblasts which is developed from resected gastric cancer tissue. Pathway enrichment analysis (PEA) of top miRNAs showed that they are significantly associated with Hippo signaling pathway (hippo pathway). The molecules relating Hippo pathway was evaluated by Western blotting in cell line, and IHC of tissue array. **Results:** PEA using top miRNAs showed the significant relationship to Hippo pathway. YAP is a final effector in this pathway, and we found that YAP is not expressed in MKN45 cells (diffuse type), which is supposed to be degraded in cytoplasm. On the contrary, MKN74 cells express both YAP and PYAP. IHC showed that YAP translocation to nucleus is significantly associated with CTGF expression. CTGF low expression is significantly associated with worse prognosis especially in diffuse type GC. (Log rank p = 0.022). This trend is similar in the analysis of patients with SGC. **Conclusions:** The role of Hippo pathway is different between intestinal type and diffuse type of GC. YAP activator could be effective for the treatment of SGC, and we are focusing on the treatment development. Research Sponsor: JSPS-KAKENHI.

**Real world prevalence of biomarkers for treatment of advanced gastric cancer or gastroesophageal junction cancer in a cohort of Colombian patients.** First Author: Diego Felipe Ballen, Instituto Nacional de Cancerología, Bogotá, Colombia

**Background:** Gastric cancer (GC) is the leading cause of cancer-related deaths in Colombia, GLOBOCAN estimated 6.451 deaths in 2022. Development of immune checkpoint inhibitors and HER2 target therapy with chemotherapy had improved overall survival in advanced setting, but we do not have data about the prevalence of biomarkers used for selection of these patients in Colombia or Latin-America. Our aim is to describe the prevalence of biomarkers used currently for selection of treatment in a real-world multicenter cohort of advanced gastric and gastroesophageal junction (GJ) cancer. **Methods:** We did a retrospective observational study of clinical information of patients treated at three reference cancer centers in Colombia between January 1, 2020 and July 31, 2021. We reviewed medical history and pathology reports looking for the prevalence of biomarkers used for selection of first line systemic therapy. Ventana 4B5 for HER2 IHC evaluation and Dako 22C3 for PD-L1 expression by IHC were used. MMR proteins were tested by IHC and nuclear expression. **Results:** 101 patients with advanced GC/GJ/EU were included. The median age was 61 years (range 18-83), 53.5% of patients were men, 92.1% were gastric and 87.1% were de novo stage IV. Signet were found in 40%, peritoneal carcinomatosis was documented in 90% and 76.2% were distal tumors (no cardial or GJ involvement). PD-L1 positivity defined as CPS ≥1 was found in 30.6%, using CPS ≥ 5 cut-off just 22.7% of them were positive. HER2 positivity and MMR deficiency were found in the same proportion of patients 5%. Among young patients (<50 years) 86% had histology, 30% were CPS ≥5, HER2 status and PD-L1 testing was unknown in 21% and 29% respectively. Conclusions: Among these real-world patients, both HER2 and PD-L1 positivity was lower than reported in other regions, Higher incidence of distal tumors, signet ring cells and histology diffuse could explain this difference. Correlation of PD-L1 positivity between 22C3 and 28.8 was unknown in our population. Our study remarks the high medical need for investigation of biomarkers and developing of prospective studies for correlation and other targets like Claudins and FGFR2b. Research Sponsor: None.

**Gastric microbiome signature to predict metachronous recurrence after endoscopic resection of gastric neoplasms.** First Author: Hokyong Lee, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea

**Background:** It is well-established that the gastric microbiota undergoes significant alterations during the process of gastric carcinogenesis. This study aimed to identify gastric mucosa-associated microbiome (MAM) for the prediction of metachronous recurrence after endoscopic resection of gastric neoplasms. **Methods:** Subgroup analyses were conducted for 61 patients (early gastric cancer: dysplasia = 55.2%) from a prospective cohort (Clinical Trials No. NCT04830618). Demographic data and histological features of Helicobacter pylori eradication therapy, endoscopic and histologic findings were incorporated. The profile of gastric MAM obtained from non-cancerous corpus biopsy specimens and was analyzed by 16S rDNA sequencing. **Results:** Over a median follow-up duration of 53.8 months, 16 metachronous gastric neoplasms (10 adenomas and 6 adenocarcinomas) developed. Baseline gastric MAM varied with H. pylori infection status, but was unaffected by the presence of atrophic gastritis, intestinal metaplasia or synchronous lesions. The group with metachronous recurrence did not exhibit distinct phylogenetic diversity compared with the group devoid of recurrence. J. diversity weighted UnFrac distance, PERMANOVA p = 0.006. In the LEfSe analysis, metachronous recurrence group had an increased abundance of Corynebacteriaceae, Comamonadaceae, Corynebacterium, Curvibacter, and a decreased abundance of Helicobacteraceae, and Helicobacter. The total study population were classified into two distinct gutotypes by baseline Gastric MAM (gastrotpe 1: Helicobacter-dominant, gastrotpe 2: Akkermansia-abundant). Gastric MAM of gastrotpe 1 had higher abundance of Helicobacter pylori, and lower abundance of Akkermansia, Comamonadaceae, Muribaculaceae, Streptococcaceae, Corynebacteriaceae, Cutibacterium. Patients in gastrotpe 2 showed higher risk of metachronous recurrence than gastrotpe 1 (hazard ratio = 4.621 by Cox proportional hazard model, p-value = 0.0185). Conclusions: Gastric cancer patients can be classified into two distinct gutotypes by their MAM profiles, which were associated with different risk of metachronous recurrence. MAM profiling of gastric cancer patients is expected to give insight into their risk of metachronous recurrence. Clinical trial information: NCT04830618. Research Sponsor: None.
Expression of claudin 18.2 in peritoneal metastasis (PM) of gastric cancer. First Author: Akira Saito, Jichi Medical University, Shimotsuma, Japan

Background: Prognosis of patients with gastric cancer (GC) with peritoneal metastasis (PM) is poor and not well understood. Claudin 18.2 is one of the main components of tight junctions that physiologically mediate cell–cell adhesion and regulate selective permeability in epithelial cellular sheets. Recent clinical trials have demonstrated that monoclonal antibodies (mAb) to CLDN18.2 have been shown to improve the outcome of the patients with unresectable metastatic GC, especially with unidifferentiated histology. However, the clinical effects of the anti-CLDN18.2 mAb for patients with PM is unclear. In this study, we evaluated the expression of CLDN18.2 in primary tumor and metastatic nodules in peritoneum of GC using immunohistochemical (IHC) staining.

Methods: In 42 patients diagnosed with stage IV GC with PM at our Department from 2014 to 2022, biopsy samples of primary tumor and peritoneal nodules were obtained and the expression of CLDN18.2 in tumor cells by IHC staining using specific antibody for CLDN18.2 (clone: 43-14A, prediluted). Ventilation was followed by this incubation with secondary antibody and the primary antibody binding visualized using the DAB IHC Detection Kit. The intensity of the membrane and cytosolic staining was classified as 0 (no reactivity), 1+ (weak), 2+ (moderate), and 3+ (strong). Samples were defined as CLDN18.2-positive when tumor cells showed specific staining with at least 1+ intensity in tumor cells. Percentage of overall CLDN18.2 positive cells was determined by the estimated number of CLDN18.2+ cells divided by the estimated overall number of tumor cells in any fractions. Her2 expression was also examined in parallel.

Results: The histology type of primary tumor was differentiated in 7, undifferentiated in 33, and unknown in 2 patients. CLDN18.2 positivity was detected in 31 (74%) of primary tumors, including 5 (71%) differentiated and 26 (79%) undifferentiated tumors. CLDN18.2 was positively detected in 15 (35%) disseminated nodules, in 4 (57%) differentiated and 11 (33%) in undifferentiated cases, respectively. All these cases also showed CLDN18.2-positive in primary sites. However, expression of CLDN18.2 in PM was not detected in 16 (35%) of undifferentiated cases and 0/7 (0%) of differentiated tumors. Moreover, strong CLDN18.2 expression (>2+) was more frequently observed in >40% of tumor cells was observed in 13 (31%) of primary tumor, but only in 2 (5%) of PM. HER2 was positive in 5 (12%) patients, and no correlation was observed between HER2 and CLDN18.2 expression. Conclusions: CLDN18.2 expression did not show significant difference depending on primary histology. Although the histology type of primary tumor was 17.8 in PM showing CLDN18.2 expression compared with that in biopsy sample of primary gastric tumor, its expression level generally decreased in PM. Investigation of CLDN18.2 expression in peritoneal nodules might be necessary to predict the clinical response of CLDN18.2 mAb for GC with PM. Research Sponsor: None.

The distribution of human epidermal growth factor receptor 2 (HER2) expression and the efficacy and safety of treatments in HER2-expressing advanced or metastatic gastroesophageal cancer (GEC): A systematic literature review (SLR). First Author: David Bing Chen, University of Washington Fred Hutchinson Cancer Center, Seattle, WA

Background: HER2 overexpression plays an important role in determining treatment options for patients with gastroesophageal cancer (GEC). HER2 overexpression has historically been defined dichotomously as HER2-positive (HER2+) or HER2-negative. An emerging potentially clinically relevant HER2 biomarker, and new treatment strategies are needed.

Methods: An SLR of PubMed, Embase, and Cochrane Central Register of Controlled Trials databases was conducted to identify clinical trials, observational studies, and meta-analyses reporting clinical outcomes or distribution of HER2 expression by IHC and ISH in advanced or metastatic (a/m) GEC. Key inclusion criteria were: English language, published between 2013-2023, reporting clinical outcomes or distribution of HER2 expression by IHC and ISH in a/m GEC. Weighted averages were calculated for the proportion of patients who were HER2+ and HER2− to estimate the proportion of patients in each HER2 expression category. Results were categorized by patient population (all GEC or gastric cancer [GC]) only. Results: Of 2,701 non-duplicated records screened, 174 studies met inclusion criteria. Distribution of HER2 expression was reported in 111 studies, 5 of which reported on the frequency of HER2 expression in IHC 1+ and/or IHC 2+ and ISH+. HER2 expression status varied by patient population, with a weighted average of 26.9% for HER2 low and 13.1-16.5% for HER2+ across groups (Table). Different cutoffs for HER2 amplification via IHC also affected the proportion of patients in each HER2 category across studies. Efficacy and safety outcomes were stratified by HER2 status or IHC results in 74 studies. However, only 3 observational studies reported outcomes separately for the HER2-low population, and results were inconclusive.

Conclusions: The distribution of HER2 expression in a/m GEC in the identified studies is highly heterogeneous, likely due to variability in IHC scoring and patient populations. Few studies with sufficient samples size (≥100 patients with HER2expression data/IHC) reported outcomes for HER2-low a/m GEC, and those that were identified of low quality. The HER2-low a/m GEC population is an important need for effective therapy. There is a need for further use of a standardized definition of HER2-low in a/m GEC and additional studies to better evaluate treatment options and outcomes for this patient population. Research Sponsor: None.

Association of methylation silencing of ULK2 via epithelial-mesenchymal transition and differentiated gastric cancers. First Author: Iori Motoo, Third Department of Internal Medicine, University of Toyama, Toyama, Japan

Background: Diffuse-type gastric cancers (DGC) typically have a poor prognosis related to their invasion and metastasis, in which the epithelial–mesenchymal transition (EMT) is the initiation step. ULK2 plays a role in the autophagy initiation, which might provide a survival advantage in cancer cells. Although knock-down of ULK2 reportedly induces autophagy and EMT in a lung cancer cell line, the mechanism of EMT via the down-regulation of ULK2, as well as its clinical significance, remains yet unclear. The present study, therefore, aims at clarifying this mechanism and its clinical significance in gastric cancers.

Methods: We examined ULK2 mRNA expression in gastric cancer tissues and normal gastric tissues of healthy people. The effects of knock-downed ULK2 were examined in two gastric cancer cell lines, which were investigated in terms of their gene expression changes by the mRNA microarray. Furthermore, to investigate the carcinogenic process from normal gastric epithelial cells, we used RGE cells, which were conditionally immortalized normal gastric epithelial cells developed from a transgenic rat. Results: ULK2 mRNA expression of gastric cancer tissues was significantly lower than that of H. pylori-negative normal tissues. ULK2 was strongly expressed in normal tissues and intestinal-type gastric cancer (ICG) but was drastically decreased in DGC by immunohistochemical staining. Furthermore, we found that the ULK2 methylation level of gastric cancer tissues was higher than that of H. pylori-negative normal tissues and ICG. Then, we validated whether knock-down of ULK2 could induce autophagy, cell migration, and EMT in NUGC3 and MKN45 cells. Using mRNA microarray analysis, we confirmed that knock-down of ULK2 changed expressions of oncogenic genes associated with cell migration and EMT. Autophagy inhibitor suppressed cell migration and EMT induced by knock-down of ULK2 in NUGC3 and MKN45. Additionally, we found that knock-down of ULK2 induced apoptosis in normal gastric epithelial cells. Conclusions: Methylation silencing of ULK2 in gastric cancer cells could induce cell migration and EMT by means of autophagy induction, causing transformation to poorly differentiated cancers. Research Sponsor: None.
De-risking 1st line chemotherapy-free immune checkpoint inhibitor (ICI) use for patients with advanced gastroesophageal cancer (aGEJ) with tumor mutational burden (TMB). First Author: Samuel J. Klempner, Massachusetts General Hospital, Boston, MA

Background: ICI + chemotherapy (chemo-ICI) is becoming an increasingly common 1st line regimen for patients with aGEJ. However, direct outcome comparison between biomarker-enriched groups receiving chemo-ICI vs. ICI monotherapy (mono-ICI) is limited in phase III trials. We sought to evaluate if TMB might identify patients for whom mono-ICI vs. chemo-ICI might be preferentially hypothesized. Patients with TMB > 10 mut/mB would have more favorable outcomes receiving ICI-chemo vs. mono-ICI and (2) patients with TMB ≤ 10 mut/mB would have diminished additional benefit from chemo-ICI vs. mono-ICI.

Methods: This study included patients with aGEJ who received 1st line chemo-ICI or mono-ICI and tumor tissue genomic profiling by Foundation Medicine. Patient data was obtained by the nationwide (US-based) identified Flatiron Health-Foundation Medicine genetic real-world clinicino-database (FH-FMI CGDB), originating from approximately 280 US cancer clinics (January 2011–March 2023). Real-world progression-free survival (rwPFS) and overall survival (rwOS) were compared between patients receiving chemo-ICI vs. mono-ICI by Cox models, adjusted by propensity scores accounting for disease stage at diagnosis, EGCG OS, PD-L1 score and microsatellite instability (MSI) status. Comparisons of the explanatory power of TMB (< 10 vs. ≥ 10 mut/mB) vs. MSI status (MSI-H vs MSI) were performed by likelihood ratio test (LRT).

Results: A total of 263 patients (176 receiving chemo-ICI and 87 mono-ICI) were included in the study. Patients with TMB > 10 mut/mB had more favorable outcomes receiving chemo-ICI vs. mono-ICI for rwPFS (median 5.8 vs. 1.9 months, hazard ratio [HR]: 0.44, 95% confidence interval [CI] 0.26–0.76, p=0.0029) and rwOS (median 11.1 vs. 7.9 months, HR: 0.68, 95% CI 0.40-0.11, p=0.1489). Patients with TMB ≤ 10 mut/mB did not have reduced benefit from mono-ICI, curiously less favorable outcomes were observed with chemo-ICI vs. mono-ICI for rwPFS (HR: 3.27, 95% CI 1.19-8.97, p=0.0212) and rwOS (HR: 3.56, 95% CI 1.14-11.08, p=0.0286). Evaluating only the mono-ICI group, the LRT indicated that when TMB was added to a model evaluating only MSI status, there was an improvement in ICI outcome prediction (p=0.006 for rwPFS and p=0.007 for rwOS). PD-L1 ≥ 10 in PD-L1 PET CT was associated with 28.91 for rwPFS (HR: 5.68, 95% CI 2.91 for rrPFS for PD-L1 ≥ 10 vs. < 10, not significant for rwOS). Conclusions: aGEJ patients with TMB > 10 mut/mB had more favorable outcomes receiving chemo-ICI vs. mono-ICI. In the TMB ≤ 10 mut/mB we did not observe more favorable outcomes among patients receiving chemo-ICI vs. mono-ICI. Curiously, we observed more favorable outcomes among those receiving mono-ICI in the TMB > 10 mut/mB group. Among patients receiving mono-ICI, TMB better predicted mono-ICI outcomes compared to MSI status alone. Research Sponsor: Foundation Medicine, Inc.

Impact of DNA mismatch repair status on prognosis of patients with locally advanced gastric cancer in a Mexican population. First Author: Maria del Consuelo Diaz Romero, Instituto Nacional de Cancerologia, Mexico City, Mexico

Background: Gastric cancer (GC) is among the five most frequent and mortal cancers in the world. In Mexico, GC is the second cause of death from cancer in men between 30 and 59 years old. The role of deficient DNA mismatch repair (dMMR)/microsatellite instability-high (MSI-H) in locally advanced gastric cancer (LACC) is still controversial. We aimed to evaluate the overall survival (OS) of patients with LACC, according to MMR status and treatment.

Methods: Retrospective study included patients from the National Cancer Institute of Mexico, with locally advanced gastric adenocarcinoma diagnosis between 2008 and 2017. The Kaplan Meier, Log Rank, and Cox Regression methods were used to analyze the relation between MMR status and overall survival in LACC. MMR status was assessed using immunohistochemistry.

Results: A total of 103 patients with LACC were enrolled for analysis. The prevalence of dMMR in GC was 13.59% (n=14). The median OS was 101.9 months in the dMMR group vs. 86.2 months in the proficient MMR (pMMR) group (HR 0.54, 95% CI 0.19-1.52, p=0.23), with a 3-year OS of 71.4 vs 66.1% respectively. Survival was also analyzed according to MMR status and choosing treatment. OS was 106.8 months in the dMMR surgery alone group, 78.4 months in the dMMR group treated with both surgery and chemotherapy, 33.1 months for pMMR group with surgery alone, and 89.2 months in the pMMR group treated with surgery plus chemotherapy (p=0.014).

Conclusions: In this analysis, OS tended to improve in dMMR group. pMMR surgery alone patients had a superior OS than other groups, while adding chemotherapy to surgery treatment seems to have a role only in pMMR patients. Research Sponsor: None.

Noninvasive assessment of programmed-death ligand-1 (PD-L1) in esophagogastric (EG) cancer using 18F-BMS-986229 PET. First Author: Samuel Louis Cytryn, Memorial Sloan Kettering Cancer Center, New York, NY

Background: PD-L1 inhibitors are now standard in advanced EG cancer, with approval often based on PD-L1 CPS. However, single biopsy sites are inadequate due to disease heterogeneity, dynamic changes over time, and variability due to operator, choice of assay, and tumor content. Better methods of non-invasive, comprehensive PD-L1 evaluation are needed.

Methods: This is a prospective, pilot PET study of the positron-emitting agent 18F-BMS-98629, a macrocyclic peptide with high affinity for PD-L1. Patients were administered 18F-BMS-98629 PET until uptake reached ≥ 60 minutes later. The primary endpoint was safety and feasibility.

Results: Ten patients underwent PD-L1 PET imaging. All had adenocarcinoma, 70% had metastatic disease, 20% had locally advanced, unresectable tumors, and 10% had resectable tumors. 30% of patients received prior treatment, including 2 with a PD-1 inhibitor. Median PD-L1 CPS was 10 (IQR 5-20). No patients experienced an adverse event associated with 18F-BMS-98629. Although PD-L1 CPS ≥ 1 was required for inclusion, 2 patients who had PD-L1 CPS ≥ 1 on initial biopsy, had a subsequent biopsy closer in time, but still prior to PD-L1 PET imaging, with PD-L1 CPS < 1. In 8 of 10 patients, the biopsy site was evaluable by PD-L1 PET imaging. 5 of the 6 biopsy sites that were PD-L1 CPS ≥ 1, were PD-L1 PET avid; both biopsy sites that were PD-L1 CPS < 1 were appropriately non-avid. In sum, 88% of patients had radiographic and pathologic concordance. The Spearman rank correlation coefficients (r_s) between PD-L1 CPS and PD-L1 PET visualization score (scored 1 to 5, defined by accumulation greater than adjacent background) was 0.64, and 0.61 between PD-L1 CPS and PD-L1 PET SUV. Patients with a higher PD-L1 PET visualization score had a higher PD-L1 CPS: those with a maximum visualization score of 5 (n=4), had a median PD-L1 CPS of 22.5 (range 5-70), those with a maximum score of 4 (n=2) had median PD-L1 CPS of 5 and 20, and those without any avid lesions (score of 3 or lower) had a median PD-L1 CPS of 5 (range 0-90). 71% of patients with PD-L1 PET avid lesions, also had non-avid sites of disease, 88% of whom had a more than 2-fold difference in SUV between the most and least avid lesions. 7 patients had untreated, advanced disease, 6 of whom were treated with PD-L1 inhibitors as frontline therapy. 3 had PD-L1 PET avid lesions: 2 achieved a complete response (CR), the third achieved a partial response (PR), and progression free survival (PFS) was 32, 28, and 22 months respectively. Among the 3 patients with non-avid PD-L1 PET imaging who received PD-L1 inhibitors as frontline therapy, 1 achieved a CR, 1 achieved a PR, and 1 had progressive disease, with PFS of 14.5, 10, and 2 months respectively.

Conclusions: We report the first use of PD-L1 PET imaging in patients with EG cancer, and demonstrate its potential use as a companion diagnostic tool to aid in identifying patients who may benefit from PD-1 therapy. Clinical trial information: NCT04161781. Research Sponsor: Bristol Myers Squibb.

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Correlation between postoperative systemic inflammatory response and prognosis in patients with advanced gastric cancer. First Author: Kenji Kuroda, Department of Gastroenterological Surgery, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

Background: Several studies have shown that postoperative infectious complications correlate with poor prognosis in various malignancies, but the prognostic significance of the postoperative inflammatory response present in the early phase of the postoperative state correlates with long-term outcomes and to identify markers in patients with advanced gastric cancer. We evaluated C-reactive protein (CRP) and white blood cell count (WBCmax) as significant and versatile markers of postoperative systemic inflammation in clinical practice that may be suitable for detecting the magnitude of inflammatory reaction. Methods: This study retrospectively reviewed 444 patients who underwent radical gastrectomy for stage II/III gastric cancer. We evaluated maximum serum C-reactive protein (CRPmax) and white blood cell count (WBCmax), defined as the maximum serum CRP level and maximum WBC count during the interval from surgery until discharge, as systemic inflammation markers. Results: In univariate analyses, CRPmax, WBCmax and infectious complications were an independent prognostic factor for OS (hazard ratio (HR) 1.69, 95% confidence interval (CI) 1.18–2.42, p=0.004) and RFS (HR 1.42, 95% CI 1.02–1.98, p=0.038), while WBCmax and infectious complications were not. Regarding the pattern of recurrence, hematogenous recurrence was significantly more frequent in the high-CRPmax group (3.8%) than in the low-CRPmax group (0.0%). Conclusions: CRPmax, which reflects the magnitude of systemic inflammation induced by surgical stress and postoperative complications in the early phase after surgery, may be a promising prognostic indicator in patients with stage II/III gastric cancer who undergo curative resection. Research Sponsor: None.

Survival trends in gastric cancer in Brazil: Real-life data from a large cancer center. First Author: Angelo Borsarelli Carvalho Brito, AC Camargo Cancer Center, São Paulo, Brazil

Background: Gastric cancer (GC) is the fourth leading cause of cancer deaths globally. There is a paucity of real-life data on GC in Brazil. Our study aimed to evaluate survival trends in gastric adenocarcinoma (GA) in a large cancer center in Brazil during 2000-2017. Methods: Based on our Hospital Cancer Registry Database, all individuals diagnosed with GA between 2000 and 2017, and treated at A.C. Camargo Cancer Center, were retrospectively included. The primary objectives were to describe the patient demographics, clinicopathological characteristics, treatment modalities, and survival trends during four separate periods of diagnosis (2000-2004; 2005-2008; 2010-2014; and 2015-2017). χ² test was performed between two specified periods (2000-2004 and 2015-2017) to compare categorical variables. Overall survival (OS) curves were stratified by four separate periods and compared with log-rank tests. Results: The current analysis comprises a retrospective cohort of 1406 patients (552 female and 854 male individuals). Across all periods, most men were aged 50 to 69 and presented with Lauren's intestinal subtype. There were significant differences between staging groups during the study. Specifically, between 2000-2004, stage IV varied from 43.6% to 32.8% in 2015-2017 (P<0.001). The most substantial variation in nonmetastatic cases occurred in stage II, comprising 9.4% of cases from 2000-2004 and rising to 24.8% in 2015-2017 (P<0.001). Concerning treatment modalities, we observed an increased utilization of a combined approach involving chemotherapy and surgery throughout the investigation. Specifically, from 2000-2004, only 12% of patients received a multimodal treatment regimen consisting of chemotherapy and surgery, whereas, between 2015-2017, this proportion increased to 36.3% (P<0.001). Also, patients receiving surgery + chemotherapy + chemotherapy varied from 12.4% of patients in 2000-2004 to 4.5% in 2015-2017 (P<0.001). When the entire cohort was analyzed, the predicted 5-year OS of patients with GA between 2000-2004 was 27.8%, which increased to 53.9% in the period from 2015-2017 (P<0.001). Among females, 5-year OS increased from 31.3% between 2000-2004 to 58.5% between 2015-2017 (P<0.001). Among males, 5-year OS increased from 25.2% to 51.0% in the same comparison (P<0.001). Conclusions: Our hospital-based data shows an upward trend in survival rates across patients with GA. We observed that 5-year OS almost doubled among men and women during the analyzed period. Recent improvements in staging methods and treatment have increased cure rates. Nevertheless, further investigation is essential to determine significant differences in OS between males and females. Research Sponsor: None.

Impact of primary prophylaxis (PP) with granulocyte colony-stimulating factor (G-CSF) on the outcomes of patients with locally advanced gastric cancer treated with FLOT: A single-center retrospective analysis. First Author: Pedro Henrique Benfato Gomes, AC Camargo Cancer Center, São Paulo, Brazil

Background: The role of primary prophylaxis (PP) with granulocyte colony-stimulating factor (G-CSF) in patients with locally advanced gastric cancer (LACG) treated with FLOT is currently unknown. Although original FLOT4 study did not recommend PP, the use of G-CSF is common in clinical practice to avoid serious complications. However, its use is associated with increased financial costs. Methods: This is a retrospective, single-institution study. We included patients with pathologically confirmed LACG who received perioperative FLOT4. Patients were categorized in two groups: PP or no-PP. Our objectives were to compare frequency of grades 3 or 4 neutropenia (G3/4N) and febrile neutropenia (FN) between PP and non-PP patients. We also evaluated the association between pathological complete response (pCR) and disease-free survival (DFS) and overall survival (OS) according to the use of PP. Binomial variables were compared using Fisher’s exact test. Kaplan-Meier method was used to calculate median DFS and OS and respective 95% confidence intervals (95%CI) and any difference assessed by the log-rank test. Results: From January 2019 until December 2022, 122 LACG patients were treated with perioperative FLOT. Median age was 56 years, 53.2% were female and 84.4% were ECOG 0. Primary prophylaxis (PP) was used by 58 patients (47.5%); there was no difference between clinical and tumor features between both groups regarding age, sex, ECOG, T and N staging and Lauren’s subtype. PP costs raised treatment costs up to 15% among patients without PP (65.6 vs. 1.7%; p<0.001). There was no difference in the frequency of FN between groups (7.8% vs. 0%; p=0.08). Overall patients, pCR occurred in 11.8% of cases. Regarding the influence of PP in pathological response after FLOT chemotherapy, there was no difference between PP and non-PP patients with pCR (14.3% vs. 9.5%, p = 0.57). Median follow-up was 27.4 (range 2.8 – 70.6 months). Twenty-six patients (21.3%) died during follow-up. Median OS was 52.5 months (95% CI: 47.5-57.8). Median OS for patients in PP and no PP groups were 44.5 and 56.2 months (log-rank P=0.15). Median DFS for patients in PP and no PP groups was 43 and 43.5 months (log-rank P=0.80), respectively. Conclusions: Despite the reduction in the frequency of G3/4N, rates of FN among patients treated with FLOT with G-CSF are too low to justify its use in a routine basis. Furthermore, PP is not associated with relevant clinical endpoints such as pCR or DFS. Based on this, PP in such situations should not be routinely used due to its financial costs. Research Sponsor: None.
ESOPHAGEAL AND GASTRIC CANCER

A randomized controlled phase III study comparing surgery alone versus adjuvant nivolumab versus adjuvant S-1 for locally advanced esophageal cancer with no pathological complete response: JCGG2206 (SUNRISE Trial).

Background: On the basis of JCOG1109, neoadjuvant chemotherapy (NAC) with Docetaxel, Cisplatin, and 5-FU (DCF) has become one of the standard treatments for locally advanced esophageal squamous cell carcinoma (LAESCC). Although the efficacy of adjuvant therapy with nivolumab after neoadjuvant chemotherapy for LAESCC has been proven by CheckMate 577, the benefits of adjuvant therapy after NAC remain controversial. Additionally, a single-arm phase II trial of adjuvant S-1 for LAESCC who received NAC demonstrated favorable outcomes and safety. Methods: Eligibility criteria include the following: thoracic esophageal squamous cell carcinoma, adenocarcinoma, or basaloid squamous cell carcinoma, reception of NAC (at most three courses of DCF or two courses of Cisplatin plus S-FU) and a diagnosis of clinical stage I (except for T1N0), II, III, IVA (except for T4), or IVB (only supraclavicular lymph node metastasis except for T4), right thoracoabdominal esophagectomy with D2 or higher lymph node dissection, R0 resection was adopted the selection design to determine the most promising regimen for the subsequent phase III trial. Patients with histologically confirmed adenocarcinoma of the stomach, adenosquamous carcinoma, or dominant histology and metastatic site, exhibiting unfavorable prognosis after surgery and adjuvant chemotherapy for patients with type 4 or large type 3 gastric cancer (JCOG2204). Protocol for open-label, randomised, controlled trial of intensive surveillance vs. standard postoperative follow-up in patients undergoing surgical resection for oesophageal and gastric cancer (SARONG trial). First Author: Sheraz Markar, University of Oxford, Oxford, United Kingdom

TPS415 Trials in Progress Poster Session

Prospective assessment of adeno/epithelial junction (AEJ) following radical resection: Real-world insights from the AEJ study. First Author: Jiabin Zheng, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China

Methods: The CLAEG study (ChiCTR190026513) is a prospective, real-world data evaluation of the clinical outcomes of patients with AEG following radical resection to investigate lymph node (LN) metastasis patterns and refine treatment strategies. Medical oncologists in China were invited to participate, if they received at least one type of AEJ operation from January 2020 to December 2021 and have completed treatment. The main endpoint of the present study was survival (OS). The median follow-up was 24.90 months. Among the 1,943 surgical indications, 1,140 were recorded as type I, 601 as type II, and 317 as type III. Laporoscopic surgery was performed in 845 patients, while 101 underwent open surgery, with no significant difference in postoperative complication rate between them. However, the laparoscopic group demonstrated superior favorable outcomes in terms of postoperative recovery times, with shorter postoperative exhaust time (3.6 days vs. 3.6 days, p < 0.001), feeding time (5.0 days vs. 5.8 days, p < 0.015), and discharge time (11.6 days vs. 14.6 days, p < 0.002), as well as lower intraoperative blood loss (103.9 ml vs. 163.4 ml, p < 0.001). Among the 891 patients who underwent transthoracic approach, while 55 underwent thoracoabdominal approach, and no significant differences in postoperative times, inpatient length of stay, and readmission rates were observed between these approaches. However, the transthoracic approach was associated with a shorter operative time (244.2 min vs. 309.3 min, p < 0.001). LN dissection was performed in all patients within the abdominal region, with additional mediastinal LN dissection in 293 patients. The LN metastasis rates were 7.0% (95% CI, 4.7% for No. 1, 1.1% for No. 2, 4.5% for No. 3, 7.8a for No. 7, 8a for No. 8, 9, 11, 19, while category-2 included No. 6, 12a, 20. Total gastrectomy was performed in 657 patients, while proximal gastrectomy was performed in 289 patients, and there were no significant differences in the rates of postoperative complications, postoperative recovery time, and hospital stay between them. However, total gastrectomy took less operation time (243.7 min vs. 258.0 min, p < 0.019) and more LNs (36.6 vs. 23.3, p < 0.001) were detected in abdomen.

Conclusion: The CLAEG study confirms the safety and feasibility of laparoscopy in AEG surgery, although its long-term oncology effectiveness requires further investigation. Transhiatal surgery is advantageous due to its shorter operation time. Both proximal and total gastrectomy can be considered as viable surgical options. AEG patients have a higher rate of abdominal LN metastasis but a lower rate of mediastinal node involvement, emphasizing the importance of precise abdominal LN retrieval. Clinical trial information: ChiCTR190026513. Research Sponsor: None.
Background: CLDN18.2 is a tight junction protein expressed in differentiated gastric epithelial cells and is abnormally expressed in various solid tumor types, serving as a promising target for therapy. To date, there are no approved therapies directed against this target, but compelling data exist using monoclonal antibodies and conventional CAR T therapy. The T Cell Antigen Coupler (TAC) technology is an approach to modifying T cells ex vivo, which allows recognition and cytotoxicity of tumor by co-expressing specific antigen and natural T cell receptor. The TAC technology has a safer profile than conventional CAR T therapies and is used to create an autologous TAC01-CLDN18.2 T cell product targeting CLDN18.2. 

Methods: This first-in-human trial (NCT05862324) is designed to assess both the safety and preliminary antitumor activity of TAC01-CLDN18.2 in patients with CLDN18.2+/HER2- solid tumors after 2 lines of therapy. The phase 1 dose escalation segment employs a traditional 3+3 dose-escalation design to evaluate increasing doses of TAC01-CLDN18.2 with estimated enrollment numbers of 9 to 24 subjects. The subsequent phase 2 will further evaluate the efficacy, safety, and pharmacokinetics of the optimal TAC01-CLDN18.2 dose. With 3 cohorts, Group A will enroll up to 57 subjects with gastric and esophageal adenocarcinoma, Group B aims to enroll 10 subjects with pancreatic ductal adenocarcinoma (PDAC) while Group C will examine up to 22 subjects with ovarian and non-small cell lung cancer (NSCLC). Groups A and C will leverage a Simon 2-stage design to assess whether the treatment achieves efficacy, while Group B will be exploratory with an opportunity for cohort enrichment based on the safety and preliminary antitumor activity of TAC01-CLDN18.2. TAC01-CLDN18.2 is a novel antibody-drug conjugate (ADC) composed of a high-affinity TF-targeting antibody and a low payload of an irreversible microtubule-disrupting payload. Groups A and B will be treated with TAC01-CLDN18.2 at levels to determine the optimal therapeutic and safety profile, and clinical activity of TAC01-CLDN18.2. Evaluation of DLTs will take place within a 28-day window following the first infusion. In both phases, CLDN18.2+/HER2- solid tumor patients must have completed at least two prior therapy lines except for PDAC patients who may qualify after one prior antineoplastic regimen. For phase 2, up to 24 patients per cohort ranging from 6 to 8 patients in each cohort. The evaluation of DLTs will be based on prospective data analysis of data from Phase 1 in association with clinical efficacy. The trial is currently in the open-enrollment stage, awaiting the inclusion of the inaugural patient. No data analysis is available as of the submission deadline. Clinical trial information: NCT05862324. Research Sponsor: None.
A phase II trial of CapeOx plus nivolumab for early relapsed HER2-negative gastric cancer (JACCRO GC-11: FirSTAR trial). First Author: Hiroki Arai, Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan.

Background: Fluoropyrimidine-based post-operative chemotherapy is one of the standard adjuvant therapies for curatively resected gastric cancer (GC).1,2 The current standard first-line chemotherapy consists of fluoropyrimidine and oxaliplatin combined with nivolumab in advanced HER2-negative GC patients including cases with a recurrence >6 months after completion of post-operative chemotherapy, based on the CheckMate 816 and ATTRACT-4 trials. However, in GC patients with early recurrence during or ≤6 months after completion of postoperative 5-FU based chemotherapy, optimal treatments remain to be established. A previous phase II study showed that capecitabine plus cisplatin is an active regimen for early relapsed GC after post-operative S-1 monotherapy. This trial aims to investigate the efficacy of capecitabine plus oxaliplatin (CapeOx) plus nivolumab for patients with early relapsed HER2-negative GC.

Methods: This is a multicenter single-arm phase II trial. The main eligibility criteria include: histologically confirmed HER2-negative adenocarcinoma of stomach or esophagogastroduodenal junction; radiologically diagnosed recurrence during or ≤6 months after post-operative chemotherapy with S-1 or S-1 plus docetaxel conducted for stage II/III GC after curative resection; age ≥18 years; ECOG performance status 0-1; having measurable lesions according to RECIST ver. 1.1; and adequate oral intake and organ functions. Enrolled patients will receive 21-day cycles of nivolumab with CapeOX at the following dose until disease progression or unacceptable toxicities: capecitabine, 1000 mg/m² twice per day on day 1-14; oxaliplatin, 130 mg/m² on day 1; and nivolumab, 360 mg on day 1. The primary endpoint is objective response rate (ORR), and the secondary endpoints include overall survival, progression-free survival, disease control rate, duration of response, and safety. PD-L1 combined positive score will be tested for the association with efficacy. We assume null ORR of 20% and alternative ORR of 32%. With two-sided alpha level of 0.05 and 90% power, sample size would be calculated as 85. Thus, a total of 92 patients are planned to be enrolled within a 2.5-year accrual period. Enrollment opened in March 2023. Clinical trial information: JRCTs01202572. 1. N Engl J Med. 2007;357:1810-20. 2. J Clin Oncol. 2019;37:1296-1304. 3. Gastric Cancer. 2018;21:81-8. Clinical trial information: JRCTs013220572. Research Sponsor: ONO PHARMACEUTICAL CO., LTD.

Phase 2 study of pembrolizumab plus lenvatinib and bevacizumab in patients with metastatic esophageal squamous cell carcinoma. First Author: Carlos Rojas, Centro de Investigacion Clinica, Bradford Hill, Santiago, Chile

Background: Initial signal finding studies demonstrated promising antitumor activity with the anti–PD-1 antibody pembrolizumab in combination with the anti-angiogenic multikinase inhibitor lenvatinib in advanced gastric and gastroesophageal junction adenocarcinoma. Because hypoxia is common in many solid tumors and is known to induce an immunosuppressive tumor microenvironment, targeting hypoxia-inducible factor-2 alpha (HIF-2α) may enhance the activity of immune checkpoint inhibitors. The ongoing phase 2 LITESPARK-016 study (NCT04796364) is evaluating the combination of pembrolizumab plus lenvatinib and the HIF-2α inhibitor belzutinib (MK-6482) in multiple solid tumors. LITESPARK-016 includes 2 esophageal squamous cell carcinoma cohorts: one enrolling patients with immunotherapy-naive and the other enrolling patients with immunotherapy-resistant esophageal squamous cell carcinoma, cohorts F and G, respectively. We report the methodology for these cohorts. 

Methods: In this phase 2, open-label, multicenter study, eligible patients in the esophageal squamous cell carcinoma cohorts have histologically or cytologically confirmed metastatic disease and have tumors that are either immunotherapy-naive with disease progression on 1 prior line of standard systemic therapy (cohort F) or immunotherapy-resistant with disease progression during or after 1 prior line of treatment that contains an anti–PD-1/PD-L1 therapy (cohort G). Patients must be aged at least 18 years, have measurable disease per RECIST v1.1 (verified by BICR) without any radiographic evidence of major blood vessel encasement or intratumoral cavitation, ECOG PS of 0 to 1, and an archival/new tumor sample for biomarker analysis. Patients in cohort F receive triple therapy with pembrolizumab plus lenvatinib plus belzutinib; patients in cohort G are randomized 1:1 to receive either the same triple therapy or double therapy with pembrolizumab plus lenvatinib. The planned starting doses are pembrolizumab 400 mg given intravenously every 6 weeks, lenvatinib 20 mg orally once daily, and belzutinib 120 mg orally once daily. Treatment will continue for up to 2 years (pembrolizumab) or until PD or discontinuation criteria are met. Approximately 30 patients will be enrolled in cohort F and in each arm of cohort G (approximately 90 total patients), with potential expansion of up to 70 additional patients in cohort F and each treatment arm of cohort G after safety/efficacy review with at least 6 months follow-up. The primary endpoints in cohorts F and G are safety (AEs, treatment discontinuation due to AEs) and ORR per RECIST v1.1 by BICR. Secondary endpoints are duration of response, disease control rate, and PFS per RECIST v1.1 by BICR, and OS. Assessment of biomarkers is an exploratory objective. Endpoints for this study are planned to be reached by November 2022 and is ongoing across 48 global sites. Clinical trial information: NCT04796364. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

A modified triplet combination of docetaxel, oxaliplatin, and fluorouracil for gastric cancer (GC) with peritoneal carcinomatosis (PC) and inoperable malignant bowel obstruction (MBO): A multi-center, non-randomized, three-cohort, phase II trial (Zhen Jing). First Author: Jian Xiao, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.

Background: For GC, PC is ranked as the most common in relapse and the second common in metastasis. MBO is a frequent and preterminal complication of PC, which has been reported to have a poor overall survival (OS) of only 3 months without effective treatment. Medical therapy of gastroenteric drainage and symptomatic drugs is the cornerstone treatment for MBO, just asimilator therapy and surgery are effective but indicated in limited patients (pts) with strict selection. Chemotherapy is the mainstay treatment for metastatic GC but its role in MBO is poorly defined. Only a few retrospective studies are available, showing conflicting results on obstruction clearance (OC) and OS. Methods: We are conducting the Zhen Jing trial in five Chinese centers to investigate the tolerability and efficacy of a dose-sense regimen of docetaxel, oxaliplatin and fluorouracil in MBO from GC. Cohort A is for pts in first-line setting. Cohort B is for second-line setting. Cohort C is for pts who failed two or more regimens. Eligible pts will receive the same experimental regimen every 28 days: docetaxel 25 mg/m² on days 1, 8, 15; oxaliplatin 85 mg/m² on days 1, 15; fluorouracil 1200 mg/m² 24-hour infusion on days 1, 8, 15. A Simon’s two-stage optimal design is applied (table below). The primary endpoint is 60-day OC rate. Secondary endpoints are 30-day GC rate, time to OC, duration, safety, overall survival and quality of life. Till July 2023, a total of 34 pts has been enrolled (16 in cohort A, 9 in cohort B, 9 in cohort C). Inclusion Criteria: 18-75 years old; Eastern Cooperative Oncology Group performance status ≤ 2; adenocarcinoma of stomach or gastroesophageal junction; peritoneal carcinomatosis established by imaging data or pathological evidence; MBO below the Treitz ligament based on clinical grounds or radiological findings; MBO with severe abdominal pain; MBO due to tumor growth; MBO less than 1 year; MBO due to tumor growth; MBO due to obstruction; MBO due to mechanical obstruction; MBO due to mechanical obstruction; MBO due to mechanical obstruction; MBO due to mechanical obstruction. Exclusion Criteria: Treated by a combination regimen containing all the study drugs; allergy to any of the study drugs; drug-2 gene overexpression; high microsatellite instability or mismatch repair deficiency; stratilized obstruction; active gastrointestinal bleeding; uncontrolled active infection; unstable heart diseases; severe lung diseases; central nervous system diseases; coexistent cerebral or meningeal metastasis; surgery or stent are required. Clinical trial information: NCT04846264. Research Sponsor: Guangzhou Shared Future Foundation.
A randomized phase II/III study to evaluate the efficacy and safety of disitamab vedotin (DV) plus toripalimab and chemotherapy/trastuzumab as first-line treatment for HER2-expressed, locally advanced, or metastatic gastric cancer. First Author: Lin Shen, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: For HER2-positive (IHC 2+/FISH-, IHC 3+) advanced gastric cancer/ gastroesophageal junctional cancer (GC/GEJ), trastuzumab in combination with chemotherapy is the standard first-line treatment. Adding pembrozumab to trastuzumab and chemotherapy significantly improves objective response rate. However, the overall survival results did not meet statistical significance. DV, a novel humanized anti-HER2 antibody conjugated with monomethyl auristatin E (MMAE) via a cleavable linker. We aimed to evaluate DV combined with toripalimab and chemotherapy/trastuzumab as first-line treatment for HER2-expressed (IHC 1+, 2+ or 3+) locally advanced or metastatic gastric/GEJ cancer.

Methods: This is a randomized, seamless phase II/III trial. Key eligibility criteria include patients confirmed GC/GEJ and systemic treatment naive. In phase II period, participants will be divided into two cohorts. Ninety participants with HER2-positive (IHC2+ FISH+ or IHC2+) will be randomly (1:1:1) assigned to receive DV every 2 weeks (Q2W) plus toripalimab Q2W and oxaliplatin and capecitabine (CAPOX) every 3 weeks (Q3W), or DV plus toripalimab and trastuzumab Q3W, versus toripalimab plus trastuzumab and CAPOX. Forty participants with HER2-low (IHC+) or IHC2+/FISH-) will be randomly (1:1) assigned to receive DV plus toripalimab and CAPOX, versus port- ipalimab and CAPOX. In phase III period, HER2-positive participants will be randomly (1:1:1) assigned to receive DV plus toripalimab or CAPOX or trastuzumab versus CAPOX plus trastuzumab = anti-PD-1 antibody, based on results from phase II, and evaluation of treatment response. HER2-low participants will be randomized to receive either DV plus Q2W toripalimab and CAPOX versus anti-PD-1 antibody based on evaluation of evolution of stand of care. The primary endpoint is PFS by IRC in PD-L1 CPS ≥5 population. To the best of our knowledge, this is the first Phase III clinical trial exploring the combination of anti-HER2 ADC and trastuzumab and chemotherapy in first-line GC/GEJ. This trial began in August 2023 and has enrolled 4 patients at the time of submission. Clinical trial information: NCT0598041. Research Sponsor: None.

A phase I study of EO-3021 in adult patients with solid tumors likely to express CLDN18.2. First Author: Meredith Pelster, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN

Background: Claudin 18 isoform 2 (CLDN18.2) belongs to a family of tight junction proteins with broad expression in gastric and gastroesophageal junctional cancer (GEJ), pancreatic, esophageal, and other solid tumors. Expression of CLDN18.2 is limited to the gastric mucosa, making it a promising antibody-drug conjugate (ADC) therapeutic target. Currently, there are no approved therapies targeting CLDN18.2. EO-3021 (also known as SYSA1801) is an ADC comprised of a fully human CLDN18.2 monoclonal antibody (mAb) specifically conjugated at glutamine 295 with a cleavable linker and MMAE with a homogenous drug-to-antibody ratio (DAR) of 2. In preclinical models, EO-3021 selectively delivers a potent cytotoxic MMAE payload directly to cancer cells expressing CLDN18.2, retains antibody-dependent cellular toxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity, and exhibits a bystander effect. In an ongoing Phase 1 study in China (NCT05099966), EO-3021 exhibited signs of anti-tumor activity in patients with gastric cancer and had an acceptable safety profile. Outside of Greater China, EO-3021 is being evaluated by Elevation Oncology for the treatment of patients with advanced or metastatic solid tumors likely to express CLDN18.2, particularly gastric and GEJ adenocarcinomas. Methods: This is a Phase I, open-label, multi-center, dose escalation and expansion study to investigate the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumor activity of EO-3021 in patients with solid tumors likely to express CLDN18.2 (NCT05980416). Patients whose tumors have progressed on or after standard therapy, or who are intolerable for available standard therapy are eligible for participation. Approximately 120 patients will be enrolled in this study. There are 4 planned dose levels in the dose finding portion of the study. Patient will receive EO-3021 intravenously (IV) once every three weeks until disease progression or unacceptable toxicity. The expansion cohort will evaluate EO-3021 in patients with gastric/GEJ adenocarcinoma. Provision of tumor samples (archived and fresh biopsy) is required for study enrollment. CLDN18.2 expression in tumor tissue via will be assessed by retrospective evaluation via central immunohistochemistry assay and preliminary correlation with tumor response. Enrollment in the dose escalation portion of the study began in August 2023. 1. Dan M, et al. Cancer Res. 83, 2023. 2. Wang Y, et al. J Clin Oncol. 41, 2023. Clinical trial information: NCT05980416. Research Sponsor: Elevation Oncology.

Phase II clinical study evaluating the efficacy and safety of disitamab vedotin combined with sintilimab and S-1 in the conversion treatment of PD-L1 overexpression unresectable gastric cancer. First Author: Han Liang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJA) is the fifth commonest cancer and the fourth leading cause of cancer deaths worldwide. In about 30% to 40% of patients with advanced gastric cancer have lost the opportunity for radical surgery at the first diagnosis, and the overall 5-year survival rate is less than 50%. In recent years, conversion therapy has shown great promise. Disitamab vedotin is an antibody-drug conjugate comprising a novel HER2-directed monoclonal antibody. In previous study C008, RC48 showed a good safety profile and promising activity towards GC, and showed equivalent efficacy for HER2 IHC 2+ or HER2 IHC 3+ tumors. Methods: This study is a single-arm, phase II trial carry out at 16 academic hospitals in China, and enroll at least 50 patients with PD-L1 CPS ≥3 in the conversion therapy for HER2 positive unresectable gastric cancer. Eligible patients are at 18 to 75 years old, histologically confirmed, unresectable stage IV GC or GEJA; Single initial unresectable factor. For peritoneal metastases (P1), Intraperitoneal free cancer cells positive (C1), Paraortic lymph node metastasis, liver metastasis (≥3 lesions, and ≤5 cm for a single lesion), ovariant metastases, and documented histologically confirmed HER2 IHC 3+ or 2+; ECOG 0-1; at least one unresectable, measurable tumor lesion according to the RECIST version 1.1; adaptable function of the heart, liver, and kidney. 30 patients will be enrolled in this trial and receive Disitamab Vedotin(2.5mg/kg, IV, Q3W), Sintilimab (200mg, IV, Q3W) and S-1 (twice daily on D1-14 are given at a dose calculate according to the body surface area and repeated every 3 weeks), until patients assessed by MDT to meet the criteria for surgical resection undergo gastroctomy. And the patients with peritoneal dissemination will combine with intraperitoneal administration of paclitaxel (60mg / m2, Q3W). The primary endpoint is R0 resection rate, Secondary endpoints include ORR, OS, RFS and safety. Seven patients have been enrolled in this study. Clinical trial information: NCT05627414. Research Sponsor: None.

SWOG S2303: Randomized phase II/III trial of 2nd line nivolumab + pacli- taxel + ramucirumab versus paclitaxel + ramucirumab in patients with PD-L1 CPS ≥1 advanced gastric and gastroesophageal adenocarcinoma (PARAMUNE). First Author: Anwaar Saeed, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Anti-VEGFR2 antibody (ramucirumab) has efficacy in gastric cancer (GC), and showed equivalent efficacy for HER2 IHC 2+ or HER2 IHC 3+ tumors. However, a significant number of patients with PD-L1 CPS ≥1 in GC or gastroesophageal adenocarcinoma (GEA) did not respond to anti-PD-1 therapy. SWOG S2303 is a randomized, open label, phase II/III trial to evaluate the efficacy and safety of nivolumab + paclitaxel + ramucirumab vs. paclitaxel + ramucirumab in PD-L1 CPS ≥1 gastric and gastroesophageal adenocarcinoma. The primary endpoint is overall response rate (ORR) defined as complete or partial response, and secondary endpoints include quality of life measured using the Functional Assessment of Cancer Therapy-Gastric (FACT-G), and showed equivalent efficacy for HER2 IHC 2+ or HER2 IHC 3+ tumors. Other endpoints include health-related quality of life measured using the Functional Assessment of Cancer Therapy-Gastric (FACT-G), and survival outcomes. This is a Phase I/II randomized, open label, phase II/III trial of 2nd line nivolumab + paclitaxel + ramucirumab versus paclitaxel + ramucirumab in patients with PD-L1 CPS ≥1, 60% of 43/63 patients for L1 CPS ≥1. Result: revealed encouraging efficacy (ORR 37.2%, 6-month PFS 46.5%) in the overall population. Median PFS and OS were found to be numerically higher in PD-L1 CPS ≥1 (6.4 months & 13.8 months respectively) compared to CPS-negative patients (5.1 months & 8.0 months), suggesting a predictive impact of PD-L1 CPS in this treatment setting. Methods: SWOG2303 is a national, randomized, open label, phase II/III trial to assess the efficacy and safety of nivolumab + paclitaxel + ramucirumab versus paclitaxel + ramu- crumab in adult patients with advanced stage MSS/pMMR PD-L1 CPS ≥1 gastric and esophageal adenocarcinoma. Notably, the addition of nivolumab to 2nd line ramucirumab plus paclitaxel was evaluated in a multi-center phase II/III trial. Study pop- ulation consisted of 60% (26/43) patients for L1 CPS ≥1. Result: revealed encouraging efficacy (ORR 37.2%, 6-month PFS 46.5%) in the overall population. Median PFS and OS were found to be numerically higher in PD-L1 CPS ≥1 (6.4 months & 13.8 months respectively) compared to CPS-negative patients (5.1 months & 8.0 months), suggesting a predictive impact of PD-L1 CPS in this treatment setting. Methods: SWOG2303 is a national, randomized, open label, phase II/III trial of 2nd line nivolumab + paclitaxel + ramucirumab versus paclitaxel + ramucirumab in adult patients with advanced stage MSS/pMMR PD-L1 CPS ≥1 gastric and esophageal adenocarcinoma. Notably, the addition of nivolumab to 2nd line ramucirumab plus paclitaxel was evaluated in a multi-center phase II/III trial. Study pop-
Organ preservation with durvalumab-based immunotherapy in combination with chemoradiation as definitive therapy for early stage, cT1, and cT2N0 esophageal adenocarcinoma with indication for radical surgery: A prospective, multicenter study of the FLOT-AIO Gastric Cancer Group (IKF-t057/ PRESTO trial). First Author: Thorsten Goetze, Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt Am Main, Germany

Background: The outcome of patients (pts) with adenocarcinomas of stomach and esophagogastric junction (GEJ) remains unsatisfactory (5-year survival rates of 24-84%), whereby surgical resection is considered as cornerstone of the curative treatment for pts with early stage esophageal adenocarcinoma (EGA), however, it is associated with mortality, morbidity and an impact on the patient’s quality of life. Recent investigations showed that in locally advanced stage EGA surgery with neoadjuvant chemoradiotherapy (CROSS trial) is beneficial over surgery alone. Further benefit was achieved for locally advanced EGA by perioperative treatment with FLOT acc. to FLOT4-trial data. Immuno-oncology (IO) therapy by using checkpoint inhibitors is approved in the palliative and adjuvant EGA situation. In this trial we aim for the organ preservation treatment of EGA pts with a combination of the anti PD-L1 antibody durvalumab- FLOT - and chemoradio-therapy. Methods: This is a multicenter, single arm, open-label, phase II trial including a total of 32 pts with T1-T2N0 EGA (including GEJ) with indication for radical surgery. Enrolled pts will receive immunotherapy with durvalumab (1500 mg Q4W) in parallel to 2 cycles FLOT (50 mg/m2 docetaxel, 85 mg/m2 oxaliplatin, 200 mg/m2 calcium folinate and 2600 mg/m2 5FU, Q2W) induction followed by 3 cycles of mFOLFOX (85 mg/m2 oxaliplatin, 200 mg/m2 calcium folinate, 400 mg/m2 5FU bolus and 1600 mg/m2 5FU over 48h, Q2W) plus concomitant radiation (25 daily fractions with 2.0 Gy = 50Gy). 8 weeks after last treatment, pts will undergo tumor assessment by esophagogastroduodenoscopy with biopsies, endoscopic ultrasonography, and CT- or MRI-scans. Surgical resection would be offered only to pts in whom a locoregional persistence is confirmed. Pts with complete remission will enter the maintenance phase and will receive durvalumab monotherapy (1500 mg, Q4W) for a maximum of 12 cycles accompanied by regular tumor re-evaluation. Primary endpoint is the rate of cCR/pCR at time of re-evaluation. Secondary endpoints include rate of cCR/pCR at 1, 2 and 3 years, rate of salvage surgery, 90 day and 1 year mortality after start of treatment, safety and quality of life. In this exploratory trial a cCR/pCR rate of ≥75% would indicate that the study treatment should be further investigated, whereas a rate < 55% indicates no further investigation. First patient was enrolled on 2023-08-28. Currently one patient is recruited. Clinical trial information: NCT05713838. Research Sponsor: AstraZeneca.
EMERALD-1: A phase 3, randomized, placeo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. First Author: Riccardo Lencioni, Department of Diagnostic and Interventional Radiology, University of Pisa School of Medicine, Pisa, Italy

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the January 20, 2024, issue of the Journal of Clinical Oncology.

433 Rapid Oral Abstract Session

Hepatic arterial infusion pump chemotherapy in patients with advanced intrahepatic cholangiocarcinoma confined to the liver: A multicenter phase II trial. First Author: Stijn Franssen, Department of Surgery, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: In the ABC-trials, the 3-year overall survival (OS) was only 2.8% for patients with advanced intrahepatic cholangiocarcinoma (ICCA) confined to the liver who received systemic gemcitabine with cisplatin. Hepatic arterial infusion pump (HAIP) chemotherapy had a pooled 3-year OS of 39.5% in a recent meta-analysis. HAIP chemotherapy involves continuous administration of fluorouracil (FUDR) directly into the hepatic artery using a subcutaneous pump. The aim of this study was to prospectively assess the effectiveness of HAIP with systemic chemotherapy in patients with advanced ICCA confined to the liver in the Netherlands. Methods: We performed a single arm phase ii trial in 3 centers in the Netherlands. Six cycles of HAIP chemotherapy with FUDR were scheduled with 8 cycles of concurrent systemic chemotherapy with gemcitabine and cisplatin, if not administered previously. The primary endpoint was OS, secondary endpoints were progression-free survival (PFS) and objective response. Results: From January 2020 until September 2022, 50 patients with advanced ICCA were included. Combined HAIP and systemic chemotherapy was administered to 38 patients (76%). Eleven patients (22.0%) received HAIP chemotherapy alone, because they had received systemic treatment before enrollment. One patient (2.0%) didn’t start treatment, because he died 19 days after pump implantation due to COVID-19. The median follow-up was 26.4 months (95% CI: 21.7 – 39.0). The median OS was 22.1 months (95% CI: 19.7 – not reached). The 1-year OS rate was 80.0% (95% CI: 69.6% – 91.9%), the 3-year OS rate was 28.6% (95% CI: 16.0% – 51.2%). The median PFS was 10.0 months (95% CI: 8.7 – 12.7). Objective response rate (ORR) was achieved in 27 patients (54.0%) and disease control at 6 months in 43 patients (86.0%). Four patients (8.0%) underwent a resection after HAIP chemotherapy of whom 2 patients had a complete pathologic response. Conclusions: Combined HAIP with systemic chemotherapy for patients with advanced ICCA was associated with favorable outcome. The median OS of 28.6% compared with 2.8% after systemic chemotherapy alone in the ABC trials. Clinical trial information: NL8234. Research Sponsor: Dutch Cancer Society (KWF).

443 Oral Abstract Session

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Background: Hepatocellular carcinoma (HCC) is the fastest-growing cancer in the US with more age-adjusted incident cases in Hispanics compared to non-Hispanics. Immigrant origin and race/ethnicity were found to be most strongly associated. Recent multinational phase III trials suggest the benefit of immunotherapies may differ based on geographic region and underlying etiology of HCC. We hypothesized that Hispanic ethnicity might influence responses to immunotherapy in HCC.

Methods: We analyzed the National Cancer Database (NCDB) to assess the impact of immunotherapy on overall survival (OS) in Hispanic patients with HCC. The database was queried for patients diagnosed with liver cancer from 2004 to 2020. Kaplan Meier method was used to assess OS and a log-rank test was used to compare survival distribution between Hispanic and non-Hispanic groups. Cox regression analysis was performed to estimate the adjusted effect of ethnicity on OS based on immunotherapy status. NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the source of the de-identified data used herein. Results: A total of 225079 patients were identified of whom 2036 patients (0.9%) received immunotherapy as first-line treatment. Patients with non-Hispanic ethnicity, male sex, who received treatment at academic/research institutions, and who were insured were more likely to receive immunotherapy. In the entire cohort, there was no difference (p=0.94) in survival between those who did not receive immunotherapy (median OS, 11.63 months; IQR: 2.79, 34.83) vs. those who did (median OS, 10.68 months; IQR: 5.19, 23.29). There were more Hispanics in the cohort who did not receive immunotherapy (12.28% vs. 10.61%). In theadr number of cases, patients without insurance were less likely to receive immunotherapy (HR: 0.87, 95% CI: 0.88-0.89; p<0.001). Among patients with immunotherapy, there was no OS difference between Hispanics (HR: 0.904, 95% CI: 0.755-1.082; p=0.971). Conclusions: Hispanics were less likely to receive immunotherapy compared to non-Hispanics. Although Hispanics had a better OS than non-Hispanics without immunotherapy, differences no longer persist among patients who received immunotherapy. These findings suggest that Hispanic ethnicity may influence responses to immunotherapy. As compared to non-Hispanic whites, Hispanics with HCC have significantly more nonalcoholic fatty liver disease and alcohol-related liver disease as contributing factors. A better understanding of the impact of immunotherapies on alcoholic and nonalcoholic liver disease-related HCC is needed. Research Sponsor: None.

Prognostic factors of gallbladder cancer (GBC) in patients diagnosed over a period of 20 years: A Canadian province experience. First Author: Nima Hamidi, University of Saskatchewan, Saskatoon, SK, Canada

Background: GBC is an uncommon but often fatal gastrointestinal cancer. The poor prognosis of GBC may in part be due to lack of effective screening tools and a delay in diagnosis that leads to presentation in the later stages of the disease. The current study aims to determine outcomes of patients with GBC in relation to contextual, demographic and clinical factors in a Canadian province over a span of 20 years. Methods: In this population-based retrospective cohort study patients with GBC diagnosed in Saskatchewan, Canada from 2000-2019 were examined. Cox proportional hazards regression analyses was performed to determine factor correlated with inferior outcomes. Results: 331 patients with median age of 74 yrs and M:F of 1:2 were identified. 92% had a pathological diagnosis of GBC & 80% had adenocarcinoma. 49% were women. Patients with stage I-II GBC had a longer OS (HR, 0.5-0.8, 5-year DFS of 68%) vs. those with stage III-IV GBC (33%). For patients with stage III-IV GBC, increased age (HR, 1.2-1.5, 5-year DFS of 38% vs. 22%), high neutrophil to lymphocyte ratio were correlated with inferior survival. Research Sponsor: University of Saskatchewan.

Relative and collective contribution of liver and bile duct cancer risk factors among minority groups in California. First Author: M. Cecilia Monge B., Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Liver and Bile Duct Cancer is a significant public health concern with higher incidence rates observed among people belonging to racial and ethnic minority groups compared to non-Hispanic White people. This study aims to understand which underlying factors contribute most to this disparity in liver and bile duct cancer among minority groups. Methods: The California Health Map database was analyzed from 2015-2017 from 58 counties, R, and p-value for each risk factor. Results of statewide demographics, cancer cases and linear regression analyses for examined variables. Data from 58 counties, R, and p-value for each risk factor’s ability to predict liver and bile duct cancer incidence rate. Significant correlations are in bold.

Results of statewide demographics, cancer cases and linear regression analyses for examined variables.

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Efficacy of immune checkpoint inhibitors in patients with HIV-associated unresectable HCC (uHCC): Propensity-score matched analyses from two international consortia. First Author: Claudia A.M. Fulgenzi, Department of Surgery and Cancer, Imperial College, Hammersmith Hospital, London, United Kingdom

Background: HIV-associated HCC is an incompletely characterized disease with poor prognosis, and health care costs and reduced quality of life associated with this paradigm have a high economic burden. Results: In the US, Europe and Asia, age-standardized incidence rates were 5.04, 4.96, and 3.28 per 100,000 person-years, respectively, and 12.05, 12.56, and 9.52 per 100,000 person-years, respectively, for the three types of liver cancer combined. Blindly assessed the MRI scans. They evaluated various MRI features and established a novel scoring system to predict resectability and outcomes based on resectability and outcomes based on resectability. All-inclusive, high agreement rates were observed in the three regions, with (ranging from 0.70-0.92). Notably, no significant differences were observed in the impact of a cirrhotic background on the diagnosis of HCC and chHCC-CC among AIEs. Furthermore, overtraining of HCC diagnosis and the diagnosis rates of the three types of liver cancer by AIEs and NIEs or trainees, independently and blindly assessed the MRI scans. They evaluated various MRI features and established a differential diagnosis encompassing HCC, chHCC-CC, and cHCC-CC. Results: The AIEs demonstrated high proficiency in utilizing MRI images exclusively for diagnosing HCC (70%-100%) and CCC (73.9%-91.3%). They significantly outperformed NIEs/trainees (all p < 0.01), achieving accuracy rates of 26.7%-66.7% for HCC and 21.7%-60.9% for CCC. However, their ability to accurately distinguish chHCC-CC (6.7%-53.3%) was limited and comparable to NIEs/trainees (26.7%-46.7%). Additionally, there was greater consistency in MRI feature assessment among AIEs for HCC and CCC when compared to cHCC-CC. Notably, no significant differences were observed in the impact of a cirrhotic background on the diagnosis of HCC and chHCC-CC among AIEs. Furthermore, overtraining of HCC diagnosis and the diagnosis rates of the three types of liver cancer by AIEs. Conclusions: MRI imaging demonstrated effective differentiation between HCC and CCC, especially when interpreted by experts in abdominal imaging. Nevertheless, the ability to accurately detect chHCC-CC was notably constrained across all participating radiologists. Consequently, this study continues to play a pivotal role in ensuring diagnostic precision and facilitating the selection of appropriate medical treatment strategies. Research Sponsor: None.

Efficacy of immune checkpoint inhibitors in patients with HIV-associated unresectable HCC (uHCC): Propensity-score matched analyses from two international consortia. First Author: Claudia A.M. Fulgenzi, Department of Surgery and Cancer, Imperial College, Hammersmith Hospital, London, United Kingdom

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Real-world (RW) characteristics, treatment patterns, and outcomes of patients with cholangiocarcinoma (CCA) treated with pemigatinib. First Author: Kira Quinney, Incyte Corporation, Wilmington, DE

Background: Pemigatinib demonstrated efficacy in fibroblast growth factor receptor (FGFR)-altered CCA in the FIGHT-202 trial; however, limited RW evidence exists on treatment patterns and outcomes in patients (pts) with CCA treated with pemigatinib. This study assessed characteristics, FGFR2 mutations, treatment patterns, and outcomes of pts treated with pemigatinib for locally advanced or metastatic CCA in the United States as part of routine clinical care. Methods: This retrospective, multi-cohort study included pts with a diagnosis of FGFR-altered locally advanced or metastatic CCA who were initially prescribed pemigatinib on or after 04/17/2020. Eligible pts were ≥18 years at pemigatinib prescription and had ≥4 months (mo) of follow-up (unless ≤4 mo due to death). Pts who received pemigatinib as part of a clinical trial or those who received systemic therapy for another primary malignancy (other than cancer of unknown primary or hepatic cancer) were ineligible. Participating physicians from Cardiac Health’s Oncology Provider Extended Network—approximately 72% from community oncology practices—abstracted data from the medical records of eligible patients into electronic case report forms. Results: Summary data were used describing descriptive characteristics. Results: Data from 120 pts (49% male; 55% White; 19% Hispanic; median age at pemigatinib prescription, 65 years) were collected from 18 physicians/practices. Testing for FGFR2 alterations was completed in 93 (n=111) of pts; of those, all but one patient (result unknown) tested positive, and 95% were tested using next-generation sequencing. At time of pemi prescription, 90% of pts had metastatic disease. Across all pts, 94% and 6% were prescribed pemigatinib as 2nd and 3rd line of therapy, respectively. The most common starting dosage was 13.5 mg daily for 14 days of 21-day cycles (87.5% of pts). Among the 60 pts who discontinued pemi during the 6.5-month median study follow-up period, 68% discontinued due to disease progression. Median RW progression-free survival (rwPFS) from date of pemigatinib initiation was 7.4 (95% CI: 6.4 – 8.6) mo. Among the 116 pts with tumor response data available, RW overall response rate (rwORR) was 61% (95% CI: 52% - 71%). Conclusions: This study complements the FIGHT-202 clinical trial by assessing the use of pemigatinib among a diverse population of patients with CCA under RW conditions. Secondaryly, the rwORR and rwPFS from this study support the clinical benefit of pemigatinib demonstrated in FIGHT-202. Research Sponsor: Incyte Corporation.

HEPATOBLIARY CANCER

466 Poster Session

Comparing first-line (1L) atezolizumab plus bevacizumab (A+B) to lenvatinib (L) or sorafenib (S) in patients with unresectable hepatocellular carcinoma (uHCC): Findings from the National Veteran Health Administration (VHA) database. First Author: David Edward Kaplan, Division of Gastroenterology and Hepatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: The approval of A+B has reshaped the treatment paradigm for patients with uHCC, establishing a new standard of care for 1L uHCC treatment. The VHA is the largest independent healthcare delivery network and the largest provider of liver-related care in the US. We aimed to compare patient characteristics and clinical outcomes between veterans who received 1L A+B and those who received 1L or S for uHCC. Methods: Using data from the VHA National Corporate Data Warehouse (1/1/2017 - 12/31/2020), we conducted a retrospective cohort study in patients diagnosed with uHCC who initiated 1L A+B after 2016. Atezolizumab plus bevacizumab (CP) scores were calculated using a previously validated algorithm. Kaplan-Meier and multivariable Cox regression methods were applied to compare overall survival (OS) between the groups. Results: We identified 405 eligible patients who received A+B, 453 received L, and 1,016 received S. Compared with patients receiving L or S, those treated with A+B had a higher proportion of CP A (47% and 35% vs. 54%, respectively; both p<0.05), a similar proportion of CP B and C (30% vs. 32%, 31%, respectively, p=0.76) and 0.68, respectively), a lower proportion of CPB (15% and 20% vs. 9%, respectively; both p<0.05), and a greater comorbidity burden as measured by the mean Charlson Comorbidity Index (CCI) (5.8, 5.8 vs. 6.6 ±4.8, both p<0.05). Median OS (mOS) was 12.8 months (95% CI: 10.6, 17.7) in the A+B cohort, compared to 9.5 months (95% CI: 7.8, 11.4) in the L cohort, and 8.0 months (95% CI: 7.8, 9.4) in the S cohort. In subgroup analyses, longer mOS was observed with A+B than with L or S in a CP A patients and those with ALBI grades 1-2A; similar mOS was observed among those with more severe liver dysfunction (Table). In multivariable analysis, A+B was associated with a 23% lower risk of death relative to others (HR=0.74, 95% CI: 0.62-0.88) and 30% lower risk of death compared to S (HR = 0.70, 95% CI: 0.60-0.82), both p<0.001. Conclusions: In a real-world VHA experience with A+B among diverse patient groups, a clinically notable survival benefit was observed with A+B compared to L or S. Future evaluations of the safety of using A+B in patients with greater liver dysfunction, including CP B and cirrhosis, are needed to support the expanded use of A+B. Research Sponsor: F. Hoffmann-La Roche.

Median Follow-up Time by Treatment Group (months)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Median Follow-up Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+B</td>
<td>12.8</td>
</tr>
<tr>
<td>L</td>
<td>9.5</td>
</tr>
<tr>
<td>S</td>
<td>8.0</td>
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</tbody>
</table>

467 Poster Session

Atezolizumab plus bevacizumab (A+B) in patients with unresectable hepatocellular carcinoma (uHCC): Real-world experience from a US community oncology network. First Author: David Cosgrove, Compass Oncology/US Oncology Network, Vancouver, WA

Background: A+B is the standard first-line (1L) treatment for uHCC based on the IMBrave150 trial, which demonstrated superior efficacy over sorafenib with longer median overall survival (19.2 vs 13.4 months) and progression-free survival (6.8 vs 4.3 months) among patients with unresectable HCC treated with (A+B) in the first line setting including patients with advanced cirrhosis. Methods: This retrospective observational study included adults who initiated 1L A+B for uHCC within The US Oncology Network between 1/1/2019 and 8/31/2022 (followed through 11/30/2022) using structural and unstructured electronic health records (EHR) based data. CP classes were reported by physicians or derived from risk factors. Kaplan-Meier methods were used to assess real-world overall survival (rwOS) and progression-free survival (rwPFS) from initiation of A+B. Exploratory subgroup analyses were conducted by CP class, albumin-bilirubin (ALBI) grade, liver disease etiology, and race/ethnicity. Results: We identified 374 patients with uHCC who initiated 1L A+B during the study period. Compared with patients enrolled in IMBrave150 (n=336), those treated with A+B in clinical practice were older (median age: 64 vs 64 years), had worse liver function (CP A: 61% vs 100%; ALBI Grade >1: 66% vs 43%), and had poorer performance status (ECOG PS: >1: 18% vs 0%). At a median follow-up of 5.6 months, 78% (n=293) had discontinued treatment. Among them, 57% discontinued was progression and 44% discontinued due to toxicity alone. Median rwOS was 13.2 months (95% CI: 9.5 – 15.0) and median rwPFS was 6.4 months (95% CI: 5.1 – 7.7). Subgroup results are shown (Table). Conclusions: In community oncology settings, 1L A+B demonstrates effectiveness in diverse patient cohorts, including those with impaired liver function, non-viral liver disease, and racial/ ethnic minorities. Predictive biomarkers can help identify subgroups who may most benefit from 1L A+B. Research Sponsor: F. Hoffmann-La Roche.
Racial/ethnic disparities in the effectiveness of atezolizumab plus bevacizumab (A+B) vs. tyrosine kinase inhibitors (TKIs) among veterans with unresectable hepatocellular carcinoma (uHCC). First Author: Daniel Eastman. Kaplan, Division of Gastroenterology and Hepatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: The etiology of liver disease and HCC often differs by race and ethnicity, which may lead to potential differential effectiveness of immunotherapy (I) by race/ethnicity. However, clinical trials for HCC have historically had limited racial diversity. Emerging data has challenged the real-world effectiveness of A+B, the standard of care for first-line (1L) uHCC. This study assessed whether there is racial/ethnic difference in the effectiveness of A+B compared to TKIs, including sorafenib (S) or lenvatinib (L). Methods: A population-based retrospective analysis was conducted using data from the Veterans Health Administration (VHA) Data Warehouse. Non-Hispanic White, African American (AA), and Hispanic patients diagnosed with uHCC between 2017 and 2022 who initiated 1L A+B (or on or after 2020), S, or L were selected. Kaplan-Meier analyses and multivariable Cox regression analysis with race/ethnicity as a treatment modifier (adjusting for age, region, etiology, TACE, ALBI class, BCLC stage, and 1L treatment) were conducted to investigate the racial/ethnic differences in the effectiveness of A+B vs S or L. Results: Of 1,738 patients, 1,180 were White (20% A+B, 56% S, 24% L), 143 were AA (22% A+B, 57% S, 21% L), and 161 were Hispanic (22% [A+B, 57% S, 21% L]). Compared to Whites, a significantly higher proportion of AAs had underlying hepatitis C (78% vs 56%; p < 0.05). There was a trend towards a lower proportion of CP B and C and less ascites in AA compared to Whites. Table shows median OS (mos) by race and region, along with hazard ratios and 95% confidence intervals (95% CI) from the multivariable survival analysis. The table is formatted as a table for clear presentation.

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Median OS (mos)</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>11.5 (10.0, 13.1)</td>
<td>(49.1, 55.2)</td>
<td>1.0 (1.0, 1.0)</td>
<td>1.0 (1.0, 1.0)</td>
</tr>
<tr>
<td>AA</td>
<td>5.0 (2.0, NR)</td>
<td>(27.9, 34.1)</td>
<td>2.0 (1.2, 3.4)</td>
<td>2.0 (1.2, 3.4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.2 (1.7, NR)</td>
<td>(27.8, 34.1)</td>
<td>3.2 (1.7, NR)</td>
<td>3.2 (1.7, NR)</td>
</tr>
</tbody>
</table>

HR [95% CI], p-value

A+B vs S: 0.69 (0.59, 0.78) [0.03] 0.60 (0.49, 0.78) [0.05] 0.55 (0.40, 0.73) [0.09]* 0.50 (0.35, 0.71) [0.03]* 0.45 (0.30, 0.68) [0.03]* 0.41 (0.28, 0.60) [0.02]*

A+B vs L: 0.74 (0.62, 0.89)* 0.77 (0.61, 0.96)* 0.70 (0.49, 1.00) 0.67 (0.36, 1.27)

Conclusions: Our study provides real-world data on treatment patterns and reports poor prognosis with pts reaching a median OS of 13.1 months. With novel agents and combination therapies being approved for uHCC, integrating them in routine care is important to improve survival. Alongside, further real-world studies are warranted for evaluating the effectiveness and outcomes of these treatments.

Real-world survival outcomes and treatment patterns in patients with unresectable hepatocellular carcinoma (uHCC): Results from the OREI05 study. First Author: Stephen Chan, Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China

Background: Recent advances in systemic therapies have revolutionized the management of HCC. However, there is limited real-world data on treatment patterns and survival outcomes in pts with uHCC. OREI05 (NCT05239507) study determined the real-world characteristics, management, and survival outcomes in pts with uHCC from 12 countries across Asia, Latin America, and Middle East and Africa. Methods: This non-interventional, retrospective study included pts with Barcelona Clinic Liver Cancer (BCLC) stage B or C unresectable or surgically resectable metastatic HCC at index date of diagnosis, diagnosed between January 2017 and December 2019. We present the clinicodemographic characteristics, treatment patterns, median overall survival (mos), landmark survival (12 and 24 months), and median progression-free survival (mPFS). Results: A total of 1,115 pts (median age 66 yrs; 59% male) were assessed, 327 pts were males. 3, 61% (425/692) were current smokers, 21.2% (155/715) used alcohol. Most common etiologies were hepatitis B (46.9% [526/1,115], hepatitis C (23.1% [260/1115]) and alcoholic liver disease (6.5% [72/1115]). At index date, 22.3% [249/1115] and 77.7% [866/1115] presented with BCLC stage B and C, respectively. S and L were the most commonly used treatment modalities (239 [21.5%] and 109 [9.9%] of 1,115). The mPFS was 6.8 mos (95% CI 6.0, 7.2) mos and mOS was 13.1 (95% CI 11.6, 14.2) mos. Conclusions: Our study provides real-world data on treatment patterns and reports poor prognosis with pts reaching a median OS of 13.1 months. With novel agents and combination therapies being approved for uHCC, integrating them in routine care is important to improve survival. Alongside, further real-world studies are warranted for evaluating the effectiveness and outcomes of these treatments.

Survival outcomes.

- mPFS (months) mOS (months) OS rates (%) (95% CI)
- Overall (N=1115) 6.8 13.1 52.7 30.7
- 12-month 1115 8.9 16.4 65.2 29.1
- 24-month 1115 9.0 15.1 66.2 20.9
- BCLC C (N=249) 8.7 15.1 64.9 24.8
- 12-month 249 9.0 15.1 64.9 24.8
- 24-month 249 9.0 15.1 64.9 24.8
- BCLC B (N=866) 7.9 13.8 55.3 25.4
- 12-month 866 9.8 15.9 65.2 23.0
- 24-month 866 9.8 15.9 65.2 23.0
- TKNs (N=889) 8.5 18.5 63.2 19.6
- 12-month 889 8.5 18.5 63.2 19.6
- 24-month 889 8.5 18.5 63.2 19.6
- ImmuneCheckpointInhibitors (N=325) 8.1 14.3 56.5 21.7
- 12-month 325 8.1 14.3 56.5 21.7
- 24-month 325 8.1 14.3 56.5 21.7
- VEGF-mAb/VEGFb-mAb (N=22) 8.0 13.3 56.7 21.7
- 12-month 22 8.0 13.3 56.7 21.7
- 24-month 22 8.0 13.3 56.7 21.7
- Combinationtherapy (N=21) 9.4 17.5 68.6 27.6
- 12-month 21 9.4 17.5 68.6 27.6
- 24-month 21 9.4 17.5 68.6 27.6

Overall survival outcomes and treatment patterns in patients with unresectable hepatocellular carcinoma (uHCC): Results from the OREI05 study. Poster Session: AstraZeneca International.
Analysis of patients (pts) with unresectable hepatocellular carcinoma (uHCC) and Child–Pugh (CP)-B liver function treated with regorafenib in routine clinical practice in the observational REFINE study. 

First Author: Yoon Jun Kim, Seoul National University Hospital, Seoul, South Korea

Background: Pts with HCC and compromised liver function are typically excluded from clinical trials. The REFINE real-world study (NCT03289273) assessed a more varied pt population treated with regorafenib than the phase 3 RESORCE trial. Median overall survival (OS) in REFINE was 13.2 months and 11.1 months in the REFINE and RESORCE trials, respectively. Treatment-emergent adverse events (TEAEs) were consistent with RESORCE. We present a subgroup analysis of outcomes in pts from CP-B with liver function.

Methods: REFINE is an international, prospective, observational study of pts with uHCC for whom the decision to treat with regorafenib was made by the physician responsible for their care. The primary endpoints were safety (Medical Dictionary for Regulatory Activities v25) and dose modifications due to drug-related TEAEs. Secondary endpoints included OS and duration of treatment (DoT). Results: Of 1005 evaluable pts, 123 (12%) were classified as CP-B at study entry, with most being CP-B7 (Table). Of the CP-B pts, 40/123 (9%), 9/123 (18%), and 59/123 (15%) initiated regorafenib at 160 mg, 120 mg, and 80 mg, per day, respectively. Median DoT with regorafenib was 2.3 months in CP-B pts and 3.7 months in the overall cohort. Incidence rates of TEAEs in CP-B pts and the overall cohort were generally similar, with drug-related in 70% and 74% of pts, respectively. Grade 3–4 TEAEs occurred in 41% of CP-B pts and 39% of the overall cohort and were drug-related in 27% and 26% of pts, respectively. Serious TEAEs were observed in 48% of CP-B pts and 37% of the overall cohort, and were drug-related in 11% and 9% of pts, respectively. Drug-related TEAEs led to less frequent dose modifications in CP-B pts than in the overall cohort (28% vs 37%), but more frequent permanent discontinuations (23% vs 16%). Median OS in CP-B pts was 6.3 (95% confidence interval [CI] 4.9, 7.8) months and in CP-B7 pts was 6.7 (95% CI 5.1, 8.7) months. Conclusions: In REFINE, pts with uHCC and CP-B liver function had similar rates of grade 3–4 TEAEs, but a higher occurrence of serious TEAEs due to underlying cirrhosis led to more frequent permanent discontinuations in CP-B pts. Median OS in CP-B pts was comparable with OS in CP-B pts overall. The evaluation of prognostic models to identify CP-B pt subgroups who may benefit from regorafenib treatment is a subject for further research. 1. Kim YJ, ILCA 2022 Reviewer: Beyer.

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First-line therapies in a Latino-rich cohort of US patients (pts) with hepatocellular carcinoma (HCC) and Child Pugh B (CPB) cirrhosis. First Author: Yameen Alfairo, Long School of Medicine, University of Texas Health-San Antonio, San Antonio, TX

Background: There are limited prospective clinical trials in patients with both HCC and CPB cirrhosis. As the prevalence of HCC and cirrhosis has risen among Latinos in South Texas, it is crucial to examine the liver dysfunction within this demographic to understand the contributing factors to treatment patterns. Therefore, we conducted a retrospective analysis of 36 patients with both HCC and Child Pugh B (CPB) cirrhosis. Methods: A cohort of 65 patients with HCC and cirrhosis from 2009–2019 was used to identify 36 patients with CPB treated at a Latino-Rich NCI-designated Cancer Center. We further segmented patients of Child Pugh Class B by ALBI grades (1-3) to explore variations in demographics, liver function, and first-line therapies. Results: Median age overall cohort is 59 (57-71); Ethnicity: Latino White (83%), Non-Latino White (14%), Black (3%). Etiology: HCV (78%) ETOH (50%), NASH (19%), and HBV (3%). ALBI Grade: I (6%), II (50%), III (44%). First line treatment in CPB: Sorafenib (86%), Nivolumab (8%), Lenvatinib (6%). Sorafenib was used across all ALBI grades, while Lenvatinib and Nivolumab were only given in ALBI II (Table). Conclusions: Sorafenib was more often given to patients with CPB cirrhosis, in the first line setting; however, more patients were treated with nivolumab or lenvatinib with ALBI II. Further investigation of survival based on ALBI levels and the trajectory of liver function over time in response to different treatment approaches is underway in a larger cohort who has received newer immunotherapy-based regimens. With more agents approved for HCC, prospective clinical trials are needed in CPB and HCC. Research Sponsor: None.

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Treatment patterns of gemcitabine-based chemotherapy in patients with de novo and recurrent advanced biliary tract cancer. First Author: Farshid Dayyani, Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, Orange, CA

Background: Biliary tract cancers (BTC) are often diagnosed at advanced stages (aBTC) when treatment options are limited. The Phase 3 TOPAZ-1 trial assessed the non-inferiority of gemcitabine and cisplatin (GemCis) versus Gem and capecitabine (GemCa) as first-line treatment in patients with de novo and recurrent patients with aBTC.

Results: A total of 580 patients were included in the analysis with either de novo or recurrent BTC (n=84) or CP-B7 (n=1005). The most common second-line therapies. Among ivosidenib-naïve patients with aBTC, 9% an IDH1 mutation, 9% an IDH2 mutation, 1% MSI-H detected, 1% FGFR2 fusions in 12% and 9% of patients with advanced CCA (acca), respectively. Here we examined the rate of molecular alteration detection using circulating tumor DNA (ctDNA) testing, treatment patterns in acca, and outcomes for patients receiving ivosidenib following ctDNA-detected IDH1 mutations. Results: Real-world data was retrieved from Guardant360INFORM, which compiles aggregated commercial payer health claims and de-identified records from ~330,000 patients with clinical ctDNA testing via Guardant360 (G360), from 2014 to 2023. Patients with acca and 1 treatment claim after G360 results were included (N=1726). First-line treatment outcomes were assessed via real-world time to treatment discontinuation (rwTDD), real-world time to next treatment (rwTTNT), and real-world overall survival (rwOS), all assessed in months. Log rank test was used to compare Kaplan-Meier survival curves. Results: Of 1495 patients with 1 ctDNA alteration detected, a guideline-recommended biomarker was identified in 18% of patients. In patients with intrahepatic CCA (n=403), 11% had an IDH1 mutation, 9% an FGFR2 fusion, 1% MSI-H detected, 1% EBB2 amplification and <1% RET fusion. Testing was performed prior to first-line therapy, after first-line therapy and after second-line therapy in 34%, 46% and 21% of patients respectively. Gemcitabine and cisplatin represented the most common first-line therapy (48%). FOLFOX (21%), gemcitabine and cisplatin (13%), and capecitabine (11%) were the most common second-line therapies. Among ivosidenib-naïve patients with an IDH1 mutation, 58 (20%) started therapy within 90 days of ctDNA test: 36% received ivosidenib, 57% received chemotherapy, 7% received other therapy. Patients with IDH1 mutations treated with ivosidenib (n=21) had numerically improved rwTDD and rwTTNT compared to those receiving chemotherapy (n=53) [rwTDD: 4.6 (95% CI:2.6-8.6) vs 2.8 (95% CI:1.2-NE); rwTTNT: 11.0 (95% CI:5.7-NE) vs 5.2 (95% CI:0.8-NE); p=0.1999 and p=0.2559]. There was no difference in rwOS between patients receiving ivosidenib or vs. However, sample size was small. Conclusions: The rate of actionable molecular alterations detected via ctDNA is 18%, comparable to reports from tissue-based testing.

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Real-world testing, treatment patterns, and outcomes following liquid biopsies in advanced cholangiocarcinoma. First Author: Amit Mahipal, University Hospitals Cleveland Medical Center, Cleveland, OH

Background: Cholangiocarcinoma (CCA) is an aggressive cancer with a poor prognosis. Given failure rates of up to 27% of CCA tissue biopsies, liquid biopsy has become an important tool to identify actionable molecular alterations. It is estimated tissue-based genotyping identifies IDH1 mutations and FGFR2 fusions in 12% and 9% of patients with advanced CCA (acca), respectively. Here we examined the rate of molecular alteration detection using circulating tumor DNA (ctDNA) testing, treatment patterns in acca, and outcomes for patients receiving ivosidenib following ctDNA-detected IDH1 mutations. Results: Real-world data was retrieved from Guardant360INFORM, which compiles aggregated commercial payer health claims and de-identified records from ~330,000 patients with clinical ctDNA testing via Guardant360 (G360), from 2014 to 2023. Patients with acca and 1 treatment claim after G360 results were included (N=1726). First-line treatment outcomes were assessed via real-world time to treatment discontinuation (rwTDD), real-world time to next treatment (rwTTNT), and real-world overall survival (rwOS), all assessed in months. Log rank test was used to compare Kaplan-Meier survival curves. Results: Of 1495 patients with 1 ctDNA alteration detected, a guideline-recommended biomarker was identified in 18% of patients. In patients with intrahepatic CCA (n=403), 11% had an IDH1 mutation, 9% an FGFR2 fusion, 1% MSI-H detected, 1% EBB2 amplification and <1% RET fusion. Testing was performed prior to first-line therapy, after first-line therapy and after second-line therapy in 34%, 46% and 21% of patients respectively. Gemcitabine and cisplatin represented the most common first-line therapy (48%). FOLFOX (21%), gemcitabine and cisplatin (13%), and capecitabine (11%) were the most common second-line therapies. Among ivosidenib-naïve patients with an IDH1 mutation, 58 (20%) started therapy within 90 days of ctDNA test: 36% received ivosidenib, 57% received chemotherapy, 7% received other therapy. Patients with IDH1 mutations treated with ivosidenib (n=21) had numerically improved rwTDD and rwTTNT compared to those receiving chemotherapy (n=53) [rwTDD: 4.6 (95% CI:2.6-8.6) vs 2.8 (95% CI:1.2-NE); rwTTNT: 11.0 (95% CI:5.7-NE) vs 5.2 (95% CI:0.8-NE); p=0.1999 and p=0.2559]. There was no difference in rwOS between patients receiving ivosidenib or vs. However, sample size was small. Conclusions: The rate of actionable molecular alterations detected via ctDNA is 18%, comparable to reports from tissue-based testing.

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Patient-reported outcomes (PROs) <65 or ≥65 years old (yo) from CARES-310: camrelizumab + rivoceranib vs sorafenib as first-line treatment for patients with unresectable hepatocellular carcinoma (HCC) - a 65 yo group favored cam + rivo. Medication TTD for jaundice was significant for sor 65 years old (baseline, overall cam + rivo n=81, sor n=61). The most common (≥5%) GAs were TP53 (38.7%) and TERT (35.5%) mutations. Neither impacted OS: median OS was 16.3 months (95% CI, 8.7 to not reached) in patients PANC and BT tumors (p=0.08), respectively. Intrahepatic cholangiocarcinoma (ICC) was the most common cancer in BT group (11.5 months vs 18.7 months, p = 0.015). In univariate analysis, PS 2.29 (1.27-4.14) 0.005 (Table 1). The most common (≥5%) GAs were TP53 (38.7%) and TERT (35.5%) mutations. Neither impacted OS: median OS was significantly lower in the afternoon group compared to the morning or mixed group (11.5 months vs 18.7 months, p = 0.015). In univariate analysis, PS 2.29 (1.27-4.14), PFS 5.6 mo [95% CI 5.5-6.3] vs 4.6 mo [3.7-5.5] (p = 0.004) and the first two cycles of ICI infusion after 1 pm (p = 0.018) were significantly correlated with OS. The first two cycles of ICI infusion after 1 pm remains an independent factor significantly associated with OS in the multivariate Cox model, with HR 2.29, 95% CI: 1.27-4.14, p = 0.005 (Table 2).

Conclusions: Our results suggest that the afternoon administration of the first two cycles of ICI is associated with lower overall survival compared to patients with advanced HCC treated by other prognostic factors. There may be confounding factors due to the variability of administration of further perfusions. Larger data are needed to confirm such findings. Research Sponsor: None.
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Poster Session

Outcomes and prognostic factors of advanced biliary tract cancers in Saudi Arabia. First Author: Kanji Alshammari, Oncology Department, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

Background: Biliary tract cancers which include gallbladder adenocarcinoma, intrahepatic and extrahepatic cholangiocarcinoma are rare, and carry a poor prognosis. This study is limited data on biliary tract cancers in the Saudi population. Methods: This single center retrospective study was conducted with data of eligible cases from the last 4 years. Survival, chemotherapy regimens, and variables such as neutrophil to lymphocyte ratio (NLR), and other potential prognostic variables were collected. Results: The study included 155 patients of which 72 had intrahepatic cholangiocarcinoma and 74 had gallbladder adenocarcinoma. The majority were females at 63% of patients. Overweight to obese patients represented 50% of the study cohort. The majority of patients (62%) had an ECOG performance status of 2 and below. Comprehensive genomic profiling was done to 20% of cholangiocarcinoma cases. Elevated CA 19-9 tumor marker (>37 micromol/L) was found in 82% of patients. De novo metastatic disease was found in 82% of patients. One third of patients (33%) were not fit for first line chemotherapy, and were given best supportive care. First line chemotherapy of platinum + gemcitabine was given to 53% of fit patients, followed by gemcitabine alone given to 38%, followed by 5-Fluorouracil chemotherapy given to 9% of patients. Very few patients lived for 12 months or more at 16%. There was a significant association between NLR and progression free survival (PFS) with median PFS being 3.5 months in the NLR >3 group (95% CI 1.2-6 months) versus median PFS of 9.8 months in the NLR < 3 group (95% CI 7.5-12 months, p=0.019). Conclusions: Biliary tract cancers still carry a poor prognosis. NLR ratio of more than 3 was found to predict a low PFS. Research Sponsor: None.

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Poster Session

Real-world use of pembidimab (pemi) for cholangiocarcinoma (CCA) among racial and ethnic minorities in the United States. First Author: Richard D. Kim, Moffitt Cancer Center, Tampa, FL

Background: Pemi received accelerated approval by the FDA in 2020 for treatment of patients (pts) with unresectable locally advanced or metastatic CCA with a fibroblast growth factor receptor 2 (FGFR2) fusion or other FGFR2 rearrangement. A recent real-world study (RWS; submitted to ASCO-GI 2022) assessing characteristics, FGFR2 testing patterns, treatment patterns, and outcomes of pts with CCA with pemi or other locally advanced or metastatic CCA in the real-world clinic care setting of one clinical care network found substantial racial and ethnic diversity in pts treated with pemi. The purpose of this analysis is to describe the findings of the pemi RWS for CCA by race and ethnicity. Methods: This was a retrospective cohort study in which US-based participating physicians from Cardinal Health’s Oncology Provider Extended Network abstracted data from eligible pts’ medical records into electronic case report forms. Eligible pts were ≥18 years of age, initially prescribed pemi for unresectable locally advanced or metastatic CCA on or after 4/17/2020, and had ≥4 mo of follow-up (pemi treatment ≥4 mo due to death). Pts who did not receive pemi or had received pemi for other systemic therapy for another primary malignancy (except for cancer of unknown primary or hepatic cancer) were excluded. Results were summarized by race (White, Black/African American, “Other” pts with mixed race or a race other than White, Black/African American, or Unknown) and ethnicity (Non-Hispanic, Hispanic) using descriptive statistics. Results: 18 physicians abstracted data for ≥10 eligible pts. Median follow-up from initial pemi prescription was 6.5 mo, at which time 71 pts (59%) were alive and 60 (50%) were still receiving pemi. The racial makeup of the study population was 55% White, 21% Black, 18% Other, and 7% Unknown. Ethnic composition was 78% Non-Hispanic, 19% Hispanic, and 3% Unknown. Key results are presented in the Table. Conclusions: The diverse population in this RWS is reflective of the heterogeneous CCA pt population in the US. These real-world overall response rates support the clinical benefit of pemi across racial and ethnic groups and complement the results of the clinical trial. Research Sponsor: Incyte Corporation.

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Poster Session

The impact of CARE Frailty Index on overall survival in older adults with hepatocellular carcinoma. First Author: Ahmet Anil Ozluk, Division of Hematology/Oncology/O’Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL

Background: Pre-treatment frailty is associated with unfavorable short and long-term outcomes among patients with hepatocellular cancer (HCC) post liver resection. However, there is a knowledge gap in identifying the subset of older adults with HCC at high risk for inferior survival outcomes. Methods: We evaluated the association between patient-reported genometric assessment (GA)-based frailty index and overall survival (OS) among older adults (≥60y) diagnosed with HCC enrolled in a single institutional prospective registry (Cancer and Aging Resilience Assessment (CARE) registry). All patients underwent a patient-reported GA at enrollment that encompassed multiple health domains related to aging. To determine frailty, we utilized a 44-item CARE Frailty Index (CARE-44) based on the principles of deficit accumulation (Giri S et al. JAGS 2021). We categorized frailty into robust, pre-frail and frail. The primary outcome was OS from the time of GA. Comparison of survival between groups was made using logrank statistic. A multivariable Cox regression model measured the independent association between frailty and OS adjusted for age, etiology, Child-Pugh score and cancer stage. Results: A total of 116 older adults with HCC were identified with a median follow-up of 1.1 year, median age was 66 (53–71) with 82% males, 27% blacks, 64% with Child-Pugh A and 78% with stage III/IV disease. Overall, 50.1% (n=58) were frail, 33.6% (n=39) pre-frail and 16.3% (n=19) robust. No significant clinico-demographic differences across the 3 frailty groups were observed. In univariable analysis, there was a marginally significant difference between the three frailty groups (p value 0.06). However, in multivariable analysis, being frail or pre-frail was associated with an increased risk of mortality (HR 2.6 [95% CI 1.03 – 6.66]; p=0.04) after adjustment for aforementioned confounders. Conclusions: Frailty status assessed by patient-reported GA using CARE-44 is associated with an increased risk of mortality in older adults with HCC. Frailty assessment should be encouraged and considered in prospective clinical trials to estimate the impact of treatment on the most vulnerable elderly. Research Sponsor: None.

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Poster Session

Real-world experience and outcomes of hepatocellular carcinoma (HCC) treated with transarterial radioembolization (TARE). First Author: Parthib Das, The Ohio State University Wexner Medical Center, Columbus, OH

Background: TARE has been the preferred choice of locoregional therapy advanced HCC in recent years. We attempted to identify factors contributing to the success of TARE in this retrospective review. Methods: HCC pts received at least one TARE between 1/1/2015 and 8/30/22 at Ohio State University were included in this study. The patient’s baseline characteristics at diagnosis (BLC) were extracted by chart review with post-procedural complications and survival outcomes. Descriptive statistics and log-rank test for survival outcomes were conducted using JMP Pro 16 (SAS Institute Inc., Cary, NC). Results: Our cohort had 144 patients with median age of diagnosis (dx) of 65 years, 81 % Caucasians, 81% males, 5% and 51% with hepatitis B and C, respectively; 24% and 21% ascites (As) and hepatic encephalopathy (HE) at dx, respectively; 72% (n=125) had just one procedure (24 had two and 23 had any). Follow-up imaging (median = 3m) was available for response evaluation in 107/144 (indeterminate response (IR) reported in 25), and the response noted was reflective of OS (objective response vs. disease progression vs indeterminate, 22 vs 6 y, p<0.001). Conclusions: Careful patient selection based on BLC and the use of ICI (before or after) could improve the outcomes in HCC patients treated with TARE. Larger prospective studies are needed to validate the study. Research Sponsor: None.
Has management of locally advanced intrahepatic cholangiocarcinocma evolved with the evidence? Trends and practice patterns from the National Cancer Database. First Author: Lauren E. Schleimer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Intrahepatic cholangiocarcinoma (IHC) is often advanced at presentation. Mounting evidence suggests a limited role for surgical resection in the setting of multifocal hepatic and regional lymph node involvement in favor of initial treatment with systemic therapy. We sought to characterize trends and practice patterns in the management of patients with IHC.

Methods: We queried the National Cancer Database (NCDB) for patients with IHC between 2004-2020. Patients with inadequate data quality, carcinoma in situ, other primary cancers prior to IHC diagnosis, distant metastasis (M1), unknown M status (MX), and no treatment were excluded. Lymph node involvement was categorized using clinic N stage to reflect clinical decision-making. Due to AJCC staging updates and coding limitations, subgroup analysis of patients with multifocal disease (T2bNXM0) in the 7th AJCC edition was confined to 2010-2017. A two-sided Cochran-Armitage test was used to evaluate time trends and Kaplan Meier methods were used to summarize overall survival (OS).

Results: Of 11,368 patients treated for IHC without distant metastasis between 2004-2020, 2467 (22%) with clinical lymph node staging had positive nodules; the subgroup with multifocal disease comprised 1,384 patients staged T2bNXM0 between 2010-2017. Overall, 36% of patients received formal resection as first treatment modality and 59% received systemic or radiation therapy first. The use of perioperative chemotherapy in combination with formal resection increased from 39% pre 2010 to 70% in 2013-2020 (p < 0.001), most often delivered post-operatively; 49% received adjuvant, 13% neoadjuvant, and 8% both in 2018-2020. Among those with clinically positive lymph nodes, there was a decreasing trend in upfront resection (p < 0.001) and an increase in systemic or radiation therapy first (p < 0.001). Similarly, in the multifocal disease subgroup analysis, the proportion of upfront formal resection trended downward from 33% in 2010 to 12% in 2017 (p < 0.001). Across the entire cohort, median OS improved from 16 months (IQR 15, 18) to 27 months (IQR 26, 29) for patients diagnosed 2018-2019 compared to < 2010. Conclusions: Over the last decade, increasing evidence has demonstrated unfavorable outcomes of surgical resection in locally advanced IHC even without distant extrahepatic disease, and supported the use of multimodality therapy. The most significant overall trends have been increasing use of perioperative systemic therapy in combination with formal resection compared to resection alone and an improvement in overall survival. On subgroup analysis, there was a significant and appropriate trend away from resection as first treatment modality for patients with clinically positive lymph nodes or multifocal disease. Research Sponsor: None.

Organ-specific response with first-line atezolizumab-bevacizumab versus lenvatinib for patients with advanced hepatocellular carcinoma. First Author: Young-Gyu Park, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related death worldwide. Immune checkpoint inhibitor (ICI)-based treatments have become the mainstay of first-line treatment for unresectable HCC, but there has been a concern that intrahepatic HCC lesions may be less responsive to ICI monotherapy. Methods: This retrospective study included 386 patients with Child-Pugh A unresectable HCC who were treated with first-line atezolizumab-bevacizumab (n = 217) or lenvatinib (n = 169). The organ-specific response was separately evaluated according to the site of the lesions: liver, lung, lymph node (LN), and intra-abdomen based on a radiological evaluation adopted from RECIST v1.1. Up to 2 lesions were chosen as target lesions in each organ for the organ-specific response evaluation. Results: The median age was 60 years. The majority of study patients were male in both groups (83.4% and 85.8% in the atezolizumab-bevacizumab and lenvatinib groups, respectively). The etiology of HCC was similar between the two groups: hepatitis B virus infection was the most common etiology in both groups (73.3% and 65.7% in the atezolizumab-bevacizumab and lenvatinib groups, respectively), while 21.2% and 29.0% of patients had non-viral HCC, respectively. Extrapathic spread was identified in 76.0% and 74.6% of patients in the atezolizumab-bevacizumab and lenvatinib groups, respectively; lung, LN, and intra-abdominal metastases were present in 39.6% vs. 39.1%, 30.0% vs. 33.1% and 16.6% vs. 15.4% of patients, respectively. The proportion of patients achieving ≥ 30% reduction in the tumor burden for each organ category was higher overall in the atezolizumab-bevacizumab group than in the lenvatinib group: 20.2% vs. 11.8%, 23.0% vs. 12.2%, 27.9% vs. 17.9%, and 33.3% vs. 15.0% for intrahepatic, lung, LN and intra-abdominal lesions, respectively. The corresponding values for the subgroup with a tumor burden ≥ 30% were more favorable 17.3% vs. 8.1%, 18.8% vs. 13.3%, 29.8% vs. 3.6% and 36.0% vs. 12.5%, respectively. Among patients with a non-viral etiology, atezolizumab-bevacizumab was not clearly associated with a better organ-specific response for the LN and intra-abdominal lesions: 20.0% vs. 54.5% and 20.0% vs. 25.0%, respectively, for ≥ 30% reduction in the tumor burden. Conclusions: Compared to lenvatinib, atezolizumab-bevacizumab was associated with a favorable organ-specific response regardless of the site of the tumor lesions. Unlike anti-PD-1 monotherapy, atezolizumab-bevacizumab had a comparable organ-specific response between intrahepatic and extrapathic lesions, especially for those with viral etiology HCCs. Research Sponsor: None.
Preoperative endoscopic biliary drainage procedures may affect intrahepatic recurrence of cholangiocarcinoma after surgical resection. First Author: Jo-Oh Kim, Soonchunhyang University Seoul Hospital, Yongsan-Gu, South Korea.

**Background:** To determine the impact of preoperative endoscopic nasal biliary drainage (ENBD) and/or endoscopic retrograde biliary drainage (ERBD) procedures on intrahepatic recurrence rate in patients with cholangiocarcinoma after surgical resection.

**Methods:** Between January 2005 and January 2023, 143 patients diagnosed cholangiocarcinoma and received surgical resection. Among 143 patients, 99 patients were treated with preoperative ENBD and/or ERBD. We retrospectively analysed prognostic factors (age; gender; preoperative ENBD and/or ERBD; tumor differentiation; TNM stage; alpha fetoprotein (AFP), CA-199, CA-125, CA-19-9, CA-15-3, CA-72-4, CEA, CA-15-3/CA-125, tumour marker level; previous treatments) and found that of who had T1/T2 factor (n=69) (P=0.168). Intrahepatic recurrence rate of patients withResponders were 1.87 mos (IQR 1.77–2.05) with a median follow-up of 18.3 mos (95% CI 17.3–19.3). The 2-year disease-free survival (DFS) rate was 57% (95% CI 43–70). Median time on therapy was 28 wks (3–69). Most treatment-related adverse events (TRAEs) were low grade, with proteinuria (33%), fatigue (20%), decreased appetite (20%), nausea/vomiting (20%), skin rash (14%), and severity of adverse events was consistent with the known profiles. Median time on therapy was 28 wks (3–69). Most treatment-related adverse events (TRAEs) were low grade, with proteinuria (33%), fatigue (20%), decreased appetite (20%), nausea/vomiting (20%), skin rash (14%), and severity of adverse events was consistent with the known profiles. For patients treated with preoperative ENBD and/or ERBD, the median time on therapy was 28 wks (3–69). Most treatment-related adverse events (TRAEs) were low grade, with proteinuria (33%), fatigue (20%), decreased appetite (20%), nausea/vomiting (20%), skin rash (14%), and severity of adverse events was consistent with the known profiles. The strut model would become the most cost-effective when the willingness-to-pay threshold exceeded $73,500/QALY. In the subgroup analysis, with the application of Asia results in the future, the model results were similar as the previous data. In the sensitivity analysis, with the variation of parameters, the results were robust. Conclusions: As one of the promising mono- or combined therapies in the first-line systemic treatment for unresectable HCC, camrelizumab plus rivoceranib demonstrated the potential to be the most cost-effective strategy, which warranted further studies to better inform the real-world clinical practices. Research Sponsor: Med-X Center for Informatics, Sichuan University.

**Results:** Results from a phase 1 study of biologic blockade of the IL-27, PD-(L)-1, and VEGF pathways with casdodzo (casdozo, SR388) in combination with atezolizumab (atezo) and bevacizumab (bev) in patients with unresectable, locally advanced, or metastatic hepatocellular carcinoma (HCC), First Author: Junji Furuse, Kanagawa Cancer Center, Yokohama, Japan.

**Background:** Casdozo is the first in class and only clinical-stage IL-27 targeting antibody, a promising immunoregulatory cytokine antagonist given in combination with atezo/bev in uHCC in the first-line systemic treatment for patients with unresectable HCC from the Chinese perspex's perspective. Methods: A Markov model was built based on global, multicenter, open-label, phase III randomized trials (Himalaya, IMbrave150, ORIENT-32, CARES-310, LEAP-002) to investigate the cost-effectiveness of tremelimumab plus durvalumab (STRIDE), atezolizumab plus bevacizumab (A+B), and camrelizumab plus nabpecizumab (C+R). Secondary cost-effectiveness analyses were performed to assess the robustness of the model. Results: The total cost and quality-adjusted life years (QALYS) of C+R, S+B, P+L, A+B and STRIDE were $12,109.27 and 0.91, $26,961.60 and 1.12, $55,382.53 and 0.83, $70,985.06 and 0.90, $84,589.01 and 0.73 respectively, resulting in the most cost-effective strategy of C+R with CER of $13,306.89 per QALY followed by S+B with CER of $24,072.86 per QALY. The S+B strategy would become the most cost-effective when the willingness-to-pay threshold exceeded $73,500/QALY. In the subgroup analysis, with the application of Asia results in the future, the model results were similar as the previous data. In the sensitivity analysis, with the variation of parameters, the results were robust. Conclusions: As one of the promising mono- or combined therapies in the first-line systemic treatment for unresectable HCC, camrelizumab plus rivoceranib demonstrated the potential to be the most cost-effective strategy, which warranted further studies to better inform the real-world clinical practices. Research Sponsor: Med-X Center for Informatics, Sichuan University.
A phase 2, open-label, safety and efficacy study of telotristat ethyl plus first-line chemotherapy in patients with advanced biliary tract cancer. First Author: Richard D. Kim, Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Patients (pts) with unresectable biliary tract cancer (BTC) have a poor prognosis. In preclinical models of cholangiocarcinoma (CCA) telotristat ethyl (TE), a tryptophan hydroxylase inhibitor that reduces production of serotonin, enhanced the antiproliferative effects of gemcitabine and cisplatin (GC) chemotherapy. This trial assessed the safety and efficacy of adding TE to GC chemotherapy in pts with advanced BTC. From March 2017 to February 2018, the 2 open-label substudies, 1 in locally advanced, or metastatic BTC, were treatment naive and had plans to initiate GC chemotherapy. On Day 1, pts received Gem 1000mg/m2 and Cis 25mg/m2 with TE 250 mg orally three times daily (TID) for 7 days. Thereafter, pts received TE 600 mg TID continuously plus GC therapy on days 1 and 8 of each 21-day cycle. The study comprised of 2 stages: stage 1 would enroll 20 patients with a safety run-in cohort in the first 6 pts to monitor safety and tolerability of TE + GC treatment for 21 days. Stage 2 would enrol 33 pts if no significant/unresolved grade 3 or higher toxicities related to study drug occurred in stage 1. The primary endpoint was 6-month (mo) progression free survival (PFS) rate according to RECIST 1.1. If 60% of pts (≥34) in the safety population were alive and progress free at 6-mos, the study was considered successful. Secondary endpoints included overall response rate (ORR) and disease control rate (DCR). Restaging occurred every 9 weeks using RECIST 1.1 and toxicities were graded using CTCAE v 5.0.

Results: Between 2019 and 2021, fifty-three pts were enrolled across 12 study sites and comprised the safety population. The majority of pts were female (62.3%) and median age was 66 yrs (range 33 to 79). Baseline mean plasma 5-HIAA was 11.1 μg/L (ULN defined as >10.8 μg/L). Thirty-one pts (58.5%) had plasma 5-HIAA levels ≤ULN and 22/53 (41.5%) had 5-HIAA levels >ULN. Majority of pts had metastatic BTC (85%) and liver was the most common primary tumor site (66%). The 6-month PFS rate was 22.6% (13/58). Based on blinded independent central review, the ORR was 13.2% and DCR was 62.3%. Mean reduction in plasma 5-HIAA at 6 mos was -1.735 μg/L (SD 8.69) in 24 patients with available data. There was no difference in 6-mo PFS rate based on pts baseline 5-HIAA status; 58% (14/24) pts had >30% decrease from baseline in 5-HIAA, however there was no correlation with 6-month PFS. The most common TE related TEAEs were constipation (28.5%), nausea (20.5%) and fatigue (22.5%)

Conclusions: Although a small patient population, TE plus GC chemotherapy was well tolerated with acceptable toxicity profile. TE provided a reduction in plasma 5-HIAA levels without correlation with 6-month PFS. The most common TE related TEAEs were constipation. As of 2022, approximately 18 pts were treated with TE plus GC chemotherapy. The ongoing study is to further evaluate the safety and efficacy of telotristat in combination with azetolcumab in azetolcumab pts with BTC. No serious safety or drug related events were observed in clinical trial phase. Clinical trial information: NCT03790111. Research Sponsor: TerSera Therapeutics.

Extension rather than early induction in S-1 adjuvant chemotherapy and prognosis in patients after biliary tract cancer resection. First Author: Kotoro Hayashi, Nagasaki University Hospital, Nagasaki, Japan

Background: The efficacy of S-1 monotherapy as adjuvant chemotherapy (AC) for pancreatic cancer has been demonstrated, and the long-term results are clearly promising. As a biliary tract cancer, the JCOG1201 trial in Japan also demonstrated the usefulness of S-1 AC recently. We have been also performed S-1 AC for biliary tract cancer in recent years in accordance with the clinical necessity. In this article, we herein retrospectively analyze the S-1 AC for biliary tract cancer especially in the significance of initiation day or therapy continuation. Methods: 134 patients with the resection of biliary tract cancer (intrabiliary cholangiocarcinoma 25, hilar 17, gallbladder 27, distant bile duct 38/papillary 25 from January 2017 to December 2021 were included in this study. Age 73(30-87) years, 47 hepatic resections/66 pancreatoduodenectomies/21 peri-gallbladder resection. The decision to administer AC was made at the discretion of the attending doctor and in consultation with the patient, and the decision to discontinue was based on the patient’s physical condition. If there was no particular need to discontinue, the treatment was continued for six months at least. Results: S-1 AC was performed in 57/137 (43%) of eligible patients. Age was similar between with or without AC patients (73 vs. 73 years old). There were no significant differences by the cancer location. Although pathological stage was higher in the patients with AC (stage 0.1:2.3:4 = 0:20:39.31%:9%) without AC (9:45:33:10:3%) (p < 0.001). 2 years recurrence free survival (2-y DFS) was similar between with or without AC patients (66.6 vs 71.6%, p=0.82). In the subgroup analysis of the patients with AC, although comparisons of induction day of AC within or after postoperative 6 weeks showed no difference in patient’s prognosis, patients with continuation of AC for at least 6 months after initiation chemotherapy had a better prognosis than without it (2-y DFS: 89.6 vs 41.7%, p<0.003).


ZSAB-TOP: A phase 2 trial of tislelizumab (TIS) and ocoiperlimab (OCI) combined with gemcitabine and cisplatin (GemCis) as the first-line treatment for advanced biliary tract cancer (BTC). First Author: Jia Fan, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Shanghai, China

Background: GemCis has long been the standard-care of advanced BTC, but the prognosis remains poor. Combinations with immunotherapy and GemCis are being explored in BTC. This study aimed to evaluate the efficacy and safety of TIS (an anti-PD-1 antibody) and OCI (a TIGIT inhibitor) combination with GemCis as the first-line treatment for advanced BTC. Herein, the primary analysis of results of this study were reported. Methods: In this open-label, single-arm, multicenter phase 2 study, systematic treatment-naive pts with unresectable advanced BTC received TIS (200 mg, day)\text{,} Q3W,OCI (100 mg/m2, Q2W) and GemCis (1000 mg/m2 and Cis 25 mg/m2 on days 1 and 8 Q2W, up to 8 cycles). The primary endpoint was investigator-assessed objective response rate (ORR) according to RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. A binomial exact test with a one-sided 0.05 was performed in the analysis of the primary endpoint to test the historical ORR of 26% with GemCis. If p≤0.05, the statistical superiority of the study treatment would be claimed. Results: A total of 45 pts were enrolled, with 75.6% having intrahepatic cholangiocarcinoma and 60.0% metastatic disease. As of 24 Aug 2023 (median follow-up, 8.0 months), 24.4 (11/45) pts remained on study treatment. Among the 41 pts in efficacy analysis set, confirmed ORR (CORR) was 48.8% (20/41), 95% CI, 32.9-65.1, p=0.0099, with 1 complete response. The statistical superiority was achieved. The subgroups of TIGIT+ pts tended to have numerically higher CORR (Table). Median PFS was 7.7 months, with 6-month PFS rate of 67.6%. Median OS was not reached, and 6-month OS rate was 86.2%. Grade ≥3 treatment-related adverse events rate was 60% (27/45). Immune-mediated adverse events rate was 37.8% (17/45), which were mostly grade 1 and 2. Conclusions: The combination of TIS and OCI combined with GemCis showed promising anti-tumor activity with manageable safety as the first-line treatment for advanced BTC. Clinical trial information: NCT05023109. Research Sponsor: None.

Poster Session

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First safety and efficacy data from phase Ib/IIa study of fostroxicabatine bralipamide (fostrox, MIV-818) in combination with lenvatinib in patients with hepatocellular carcinoma (HCC). First Author: Maria Reig, Hospital Provincial Clinic de Barcelona, Barcelona, Spain

Background: Fostrox is an orally administered troxoracicabatine-based nucleotide prodig in clinical development in combination with lenvatinib (NCT03781934). Fostrox is rapidly metabolized by human hepatocytes, direct high levels of the active metabolite to the liver. Phase 1 fostrox monotherapy demonstrated selective in vitro-renal activity in on-treatment liver biopsies. The anti-angiogenic activity of lenvatinib has the potential to synergize with fostrox by hypo-xia-induced increase in the expression and activation of the active metabolite of fostrox in the tumor. Methods: In a phase Ib/IIa study with an intermittent dose escalation 3+3 cohort design followed by a dose expansion phase, fostrox was administered orally QD for 5 days in 21-day cycles in combination with lenvatinib according to local prescription information. Patients (pts) with Child-Pugh A, >18 years, ECOG PS = 1 and adequate organ function were enrolled. The primary objective was to assess safety, tolerability and PK. Secondary endpoints included pharmacokinetic (PK) and pharmacodynamic effects of fostrox in combination with lenvatinib.

Results: At interim data cut-off 18 pts (6 pts in Ib and 12 pts in IIA) were enrolled at fostrox QD doses of 20mg (3 pts) and 30mg (15 pts) in combination with lenvatinib. Median age was 63 years (range: 42-82). No DLTs and the only discontinuation of fostrox due to AEs with a median FU of 3.8 months, were observed. Most common grade 3/4 AEs were neutrophil count decrease, platelet count decrease and febrile neutropenia, bleeding events or proteinuria were reported. The safety profile was consistent with each individual agent. In phase Ib, central independent review based on RECIST 1.1 showed SD in 5/6 pts, while mRECIST showed CR in 1 pt, PR in 2 pts and SD in 2 pts. Updated lab data and efficacy of fostrox by phase IIA by independent review together with PK for fostrox and lenvatinib, and liver biopsy biomarker data, will be presented. Conclusions: Fostrox in combination with lenvatinib, in pts with HCC who progressed on previous systemic treatment, had an acceptable safety and tolerability profile with promising interim efficacy results from the recently completed phase Ib/IIa study. Clinical trial information: NCT03781934. Research Sponsor: Medivir AB.

The efficacy and safety of transarterial chemoembolization combined with cadonilimab and lenvatinib for unresectable hepatocellular carcinoma: A phase II clinical trial. First Author: Guo Liang, Department of Interventional Therapy, Zhejiang Cancer Hospital, Hangzhou, China

Background: Immune-checkpoint inhibitors, in combination with targeted therapy and local therapy, have been developed as promising treatment for unresectable hepatocellular carcinoma (HCC). However, their administration poses the risk of immune-related adverse events (irAEs). Research Sponsor: Japan Agency for Medical Research and Development.

Methods: This is a phase II investigator-initiated trial involving 2 academic centers in Korea. Key eligibility criteria include contraindication of HCC; prior treatment with Atexo-Bev at least ≥ 2 cycles; Child-Pugh A; ECOG performance status 0-1. Eligible patients received cadonilimab 160 mg once daily 3 weeks on/1 week off until progressive disease or intolerable toxicity. The primary endpoint is progression-free survival (PFS). Secondary endpoints were objective response rate (ORR), disease control rate (DCR) according to both RECIST v1.1, overall survival (OS) and treatment-related adverse event (TRAE). Results: Total 40 pts were enrolled from Dec 2021 to May 2023. Pts characteristics were as follows: median age of 56 (range, 36-81); hepatitis B (77.5%), hepatitis C (10.0%), non-viral (12.5%); BCLC stage (97.5%); and AFP <400 ng/ml (40.0%). As of the date of data cut-off (15 Aug 2023), the median follow-up duration was 6.6 mo (95% CI, 5.0-8.2). The median PFS was 3.5 mo (95% CI, 3.0-4.0); ORR and DCR were 10.0% and 82.5%. The median OS was 9.7 mo (95% CI, 8.3-11.1) and 6-month OS rate was 55.0%. The median OS since the start of prior Atexo-Bev was 16.6 mo (95% CI, 11.9-21.3). When stratified according to the duration of prior Atexo-Bev (<4 cycles vs >4 cycles), the median OS was not reached vs 3.6 mo; p=0.001 and ORR (13.3% vs 0%; p=0.009), while there was a trend for better median PFS (3.8 mo vs 2.5 mo; p=0.107). The most common 3-grade TRAEs were thrombocytopenia (5.0%), palmar-plantar erythrodysthesia (2.5%), and fatigue (2.5%). Conclusions: Cadonilimab was effective as second-line therapy in HCC pts who progressed on first-line Atexo-Bev. Efficacy and safety outcomes from our study were consistent with those observed in the pivotal phase 3 RESORCE trial which included sorafenib-tolerated/progressed pts. Clinical trial information: NCT01345332. Research Sponsor: Bayer.
Lenvatinib plus pembrolizumab versus lenvatinib alone as first-line therapy for advanced hepatocellular carcinoma: Long-term efficacy and safety results from the phase 3 LEAP-002 study. First Author: Richard S. Finn, University of California, Los Angeles, Los Angeles, CA

Background: The randomized, double-blind, phase 3 LEAP-002 study (NCT03713599) was conducted to evaluate the efficacy and safety of first-line (1) lenvatinib (len) + pembrolizumab (pembro) vs len + placebo (pbo) in patients (pts) with advanced hepatocellular carcinoma (HCC). After a median follow-up (randomization to data cutoff) of 32.1 mo, LEAP-002 did not meet its primary endpoint of OS at final analysis (median, 21.2 vs 19.0 mo; HR, 0.840; 95% CI, 0.708-0.987) and PFS at interim analysis (1:1:1; median, 8.2 vs 8.9 mo; HR, 0.811; 95% CI 0.734-1.024). However, the study highlighted the activity of len + pembro and, given the late separation of Kaplan-Meier survival curves for OS and PFS between treatment arms from 12 mo onwards, outcomes with extended follow-up are of interest. We report results after 12 mo of additional follow-up (median 43.6 mo). Methods: Eligible pts with advanced HCC were randomized 1:1 to len (8 mg/day if bodyweight [BW] < 60 kg; 12 mg/day if BW ≥ 60 kg) + pembro (200 mg IV Q3W) or len + pbo. Dual primary end points are ORR and DOR, both per RECIST v1.1 by BICR. Secondary end points included ORR and DOR, both per RECIST v1.1 by BICR, and safety. Data cutoff was June 6, 2023. Results: 794 pts were randomly assigned to receive len + pembro (n = 395) or len + pbo (n = 399). Median follow-up was 43.6 mo (range, 37.3-52.6), and treatment was ongoing in 25 (32%) pts. Median OS was 21.1 mo with len + pembro vs 19.0 mo with len + pbo (HR, 0.836; 95% CI, 0.713-0.968). OS rates for len + pembro vs len + pbo were 43.4% vs 40.0% at 24 mo, 32.7% vs 24.3% at 36 mo, and 22.4% vs 15.3% at 48 mo. Median PFS was 8.2 mo with len + pembro vs 8.13 mo with len + pbo (HR, 0.810; 95% CI, 0.692-0.949). PFS rates for len + pembro vs len + pbo were 16.4% vs 9.7% at 24 mo and 14.1% vs 3.3% at 36 mo. ORR was 26.3% for len + pembro vs 17.5% for len + pbo. Median DOR was 16.6 mo (range, 2.0+ to 45.3+), for len + pembro vs 10.4 mo (range, 1.9+ to 37.0+), for len + pbo. Grade 3-5 treatment-related adverse events (TRAEs) rates were less when len + pembro vs len + pbo. No additional deaths due to TRAEs were reported. The most common TRAEs of any grade in the len + pembro vs len + pbo groups were hypertension (43.8% vs 46.8%), diarrhea (40.9% vs 34.2%), and hyperglycemia (40.0% vs 35.5%). Overall, 46.6% vs 55.5% of pts received ≥1 poststudy systemic antitumor treatment. Conclusions: With an additional 12 mo of follow-up, the LEAP-002 primary endpoint of OS and PFS for len + pembro vs len + pbo remained consistent with the primary efficacy analyses; no new safety signals were observed. These results support len + pembro as a promising therapy for pts with advanced HCC, with len + pembro retaining its role as a standard of care treatment in 1L advanced HCC. The activity of len + pembro for pts with advanced HCC observed in this study supports the evaluation of TACE vs len + pembro for intermediate-stage HCC in the ongoing phase 3 LEAP-012 trial (NCT04264177). Clinical trial information: NCT03713599. Research Sponsor: Eisai Inc., Nalley, NJ, USA, and Merck & Co., Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
Coformulated quavonlimab and pembrolizumab (pembro) in combination with lenvatinib (lenva) as first-line (1L) therapy for patients (pts) with advanced hepatocellular carcinoma (HCC): Phase 2 KEYS-P004 study
First Author: Lorenza Rimassa, Department of Medical Sciences, Humanitas University, Pieve Emanuele & Humanitas Cancer Center, IRCCS Humanitas Research Hospital Rozzano, Milan, Italy
Background: Combinations of a PD-1/L1 inhibitor with a CTLA-4 or VEGF inhibitor have been approved as 1L treatment options for pts with advanced HCC. The multicenter, phase 2 KEYS-P004 study (NCT04740307) was conducted to evaluate the coformulation of quavonlimab (CTLA-4 inhibitor) and pembro (PD-1 inhibitor) in combination with lenvina (multityrosine kinase inhibitor) as 1L treatment for pts with advanced HCC. Methods: Pts were ≥18 y of age, had histologically or radiographically confirmed HCC with no prior systemic therapy, and were not amenable to curative therapy; had Child-Pugh A and ECOG PS 0-1. The study consisted of a safety lead-in phase (approximately 6-20 pts) to evaluate the tolerability of the recommended phase 2 dose of lenva with a possibility of dose modification based on dose-limiting toxicities (DLTs) and an efficacy expansion phase (approximately 110 pts). In the safety lead-in phase, pts received a fixed-dose coformulation of quavonlimab 25 mg and pembro 400 mg IV Q6W in combination with lenva 8 mg (body weight [BW] <60 kg) or 12 mg (BW ≥60 kg) PO QD. Allocation to the efficacy expansion phase was allowed if the doses of lenva were determined to be tolerable. Primary end points were ORR per RECIST v1.1 by BICR and safety. Secondary end points included DOR, DCR, and PFS per RECIST v1.1 by BICR and OS.
Results: No DLTs were observed in the 6 pts enrolled in the safety lead-in phase. 115 pts in the safety lead-in phase or the efficacy expansion phase were treated with the fixed-dose coformulation of quavonlimab and pembro plus lenva 8 or 12 mg. 94 pts (81.7%) were male, median age was 64 (range, 32-83), and 80 pts (69.6%) had AFP >400 ng/mL. Of the June 22, 2023, data cutoff date, 65% (49/75) had prior locoregional treatment, and 70% (65/93) had prior systemic therapy. 31 pts progressed on prior systemic therapy. Median PFS and OS were 8.2 mo (95% CI, 6.2-10.2) and 22.1 mo (95% CI, 15.6-not reached), respectively; 12-mo PFS and OS rates were 32.2% and 65.2%, respectively. Treatment-emergent adverse events (TEAEs) occurred in 109 pts (84.8%); most common (≥25%) were hypertension (35.7%) and diarrhea (27.8%). Grade 3-5 TEAEs occurred in 66 pts (57.4%); most common (≥5%) were hypertension (8.7%) and immune-mediated enterocolitis (7.0%). 8 pts (7.0%) died due to AEs; 2 were considered treatment related (acute respiratory failure and subarachnoid hemorrhage). Efficacy and safety of surufatinib in biliary tract cancer: Preliminary results
First Author: Zongli Zhang, Qilu Hospital of Shandong University, Jinan, Shandong, China
Background: When applied in the second-line treatment for biliary tract cancer (BTC) pts, surufatinib (a small-molecule inhibitor of VEGFR1-3, FGFR1 and CSF-1R) monotherapy demonstrated manageable tolerability and safety profiles. This study was to evaluate the efficacy and safety of surufatinib as a therapy for BTC in a real-world setting. In particular, pts who received prior treatment were allowed. Methods: This is an ongoing single-arm, multi-center, open-label real-world study conducted in China. The study would enroll 200 pts with unresectable or surgical resection with positive margins BTC. Pts would receive surufatinib with or without combination as adjuvant (namely pts with positive margin after resection), first- or further-line therapy, at a proper dose (200-300mg) judged by physicians once per day in 28-day cycles. The primary endpoint is relapse-free survival (RFS) for pts whose primary lesions were resected, and progression-free survival (PFS) for those that had evaluable lesions. If available, tumor assessments were performed every 2 cycles ≤7 days according to RECIST version 1.1. Results: By Sep 10, 2023, 56 eligible pts had been enrolled, of whom 16 (28.6%) were female. The median age was 64 (range: 49-78) y, 24 (42.9%), and 4 (7.1%) pts received surufatinib as adjuvant, first-line, and above, respectively. As to location, 23 cases were intrahepatic cholangiocarcinoma (ICC), and 33 cases were extracholangiocarcinoma (ECC) or gallbladder cancer (GBC). With a median follow-up time of 9.5 months (range: 1.1-20.3) mo, the global ORR was 10.4% (95% CI: 0.9-13.9) mo. The mRFS of pts who received surufatinib as adjuvant treatment was 11.3 (95% CI: 10.4-NA) mo, and mPFS of those who received surufatinib as systematic treatment was 9.0 (95% CI: 7.8-10.8) mo. Pts with ICC demonstrated an mRFS/mPFS of 10.4 (5.8-NA) mo, and those with ECC or GBC demonstrated 10.4 (5.9-NA) mo. The global mOS was 15.8 (12.4-NA) mo. Among those with ICC who were previously untreated (n=28), 5 pts (17.9%) achieved CR, 10 (35.7%) pts PR, 16 (57.1%) pts SD, and 5 (17.9%) pts suffered PD. The ORR was 25.0%, and DCR was 82.1%. No new safety signal was observed. Conclusions: Surufatinib exhibited promising efficacy and manageable toxicity on pts with BTC in the real-world setting. Clinical trial information: NCT05064852. Research Sponsor: None.
Efficacy and safety of brigimadlin (BI 907828), an MDM2 antagonist, in patients (pts) with advanced biliary tract cancer: Data from two phase IIa/b dose-escalation/expansion trials. First Author: Teresa Macarulla, Gastrointestinal and Endocrine Tumor Unit Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain
Background: Patients with advanced biliary tract cancer (BTC) have a 1-year survival rate <10%. Brigimadlin (BI 907828) is an MDM2 antagonist that blocks the MDM2–p53 interaction, thereby restoring p53 activity and leading to cell-cycle arrest and apoptosis in TP53 wild-type tumors. Brigimadlin is currently being assessed in two Phase Ia/b dose-escalation/expansion trials in pts with advanced/metastatic solid tumors as monotherapy (NCT03449581) and in combination with an anti-PD-1 antibody, ezabenlimab (NCT03964233). Here, we present data in pts with advanced BTC treated in these trials. Methods: Pts in the monotherapy trial received escalating doses of brigimadlin on day 1 of 21-day cycles (Q2W). Pts in the combination trial received escalating doses of brigimadlin and 240 mg ezabenlimab on day 1 Q2W (doublet), one pt also received the anti-LAG-3 antibody BI 754111 (which has since been discontinued; triplet). Results: At data cut-off (June 2023), a total of 16 pts with BTC have been enrolled (10 in the monotherapy and 6 in the combination trial). In the monotherapy trial, 9 pts received brigimadlin 45 mg Q2W and 1 received 80 mg Q2W. In the combination trial, 5 pts received 30 mg/45 mg brigimadlin doublet and 1 received 45 mg triplet. Across both trials, 7 pts with MDM2-amplified tumors achieved partial response (PR), 3 in the monotherapy trial and 4 in the combination trial. In the monotherapy trial, the responding pts had intrahepatic cholangiocarcinoma (ICC; 80%, 73% tumor shrinkage, progression-free survival [PFS] 13.9 months), gallbladder adenocarcinoma (80%, 73% tumor shrinkage, PFS censored at 66 days), and cholangiocarcinoma (45%, 68% tumor shrinkage, PFS censored at 164 days). In the combination trial, 3 responding pts had ICC (pt 1, 30 mg doublet, 54% tumor shrinkage, PFS 6 months; pt 2, 45 mg doublet, 49% tumor shrinkage, PFS 7 months; pt 3, 45 mg doublet, 39% tumor shrinkage, PFS censored at 5.5 months) and 1 had gallbladder cancer (45 mg doublet, 50% tumor shrinkage, PFS 7.9 months). A further 7 pts (5 in the monotherapy trial and 2 in the combination trial) achieved stable disease (SD). In both trials, the most common any-grade treatment-related AE (TRAE) was nausea; the most common grade ≥3 TRAEs were thrombocytopenia and neutropenia. Conclusions: Brigimadlin showed a manageable safety profile and encouraging preliminary efficacy in pts with BTC, with 7 PRs and 7 SDs in 16 pts. A Phase IIa/b trial of brigimadlin in patients with MDM2-amplified, TP53 wild-type BTC and other solid tumors is ongoing (Brightline-2). Clinical trial information: NCT03449581 and NCT03964233. Research Sponsor: Boehringer Ingelheim.
A single-arm, multi-center phase II study of tislelizumab combined with lenvatinib and GEMOX as conversion therapy in potentially resectable locally advanced biliary tract cancer (ZSAB-TransGOLP): A primary analysis\textsuperscript{1}.

First Author: Jia Fan, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Shanghai, China

Background: We have previously reported that GEMOX combined with lenvatinib and PD-1 antibody (GOLF regimen) showed promising efficacy as first-line treatment for advanced intrahepatic cholangiocarcinoma (CCA), indicating that GOLF regimen may be an ideal conversion therapy for patients (pts) with potentially resectable advanced biliary tract cancer (BTC). This phase II trial explored the efficacy and safety of GOLF as conversion therapy in potentially resectable and locally advanced BTC.

Methods: Patients with potentially resectable locally advanced BTC were enrolled and received tislelizumab (300mg, Q3W) and lenvatinib (8mg, QD) and GEMOX chemotherapy (Q3W), including gemcitabine 100mg/m\textsuperscript{2} on day 1, 8 and oxaliplatin 85mg/m\textsuperscript{2} on day 1. Tumor responses were evaluated every 9 weeks according to RECIST v1.1, and the resectability was subsequently discussed by MDT. For pts who were eligible for surgery, capectabine alone was administered as adjuvant therapy after radical surgery. Pts who was not suitable for surgery continued to the original treatment regimen until progression or intolerable toxicity. The primary endpoint was R0 resection rate, and secondary endpoints included ORR, DCR, DFS, OS, CPR, MPR, RFS.

Results: From December 2021 to July 2023, 41 pts were enrolled, 21 males and 20 females with a mean age of 57 years. 87.8% pts had HCC, 3.7% had perihilar bile duct cancer and 4.9% had gallbladder cancer. TMM stage was II, IIIA, IIIC and IIIC for 2.4%, 34.1%, 58.5% and 4.9% of pts respectively. At cut-off date (September 10, 2023), the mean follow-up was 7.7 months, 39 pts completed at least three cycles of conversion therapy and 7 pts still administered with scheduled conversion therapy. The ORR was 43.9% (18/41) and the DCR was 87.8% (36/41). The median duration of therapy before surgery was 2.9 months (95\% CI: 2.6-6.4), R0 resection rate was 48.8% (20/41), and 2 pts underwent R1 resection. 9.1% (2/22) pts had a pCR and 22.7% (5/22) had an MPR. The most common grade 3/4 treatment-related adverse events (TRAEs) included neutropenia (31.7%), increased GGT (19.5%), leukopenia (12.2%). No grade 5 AEs occurred.

Conclusions: This study demonstrates the high effectiveness and manageable safety of GOLF regimen as conversion therapy for potentially resectable locally advanced BTC. Survival data will continue to be followed up. Clinical trial information: NCT05156788. Research Sponsor: None.

Therapeutic effectiveness of high-intensity focused ultrasound (HIFU) ablation in patients with unresectable hepatocellular carcinoma. First Author: Jin Il Kim, The Catholic University, Seoul, South Korea

Background: High-intensity focused ultrasound (HIFU) ablation is a new therapeutic method for treatment of solid tumor. To determine the efficacy and safety of HIFU, we report our experience for local therapy of primary and metastatic hepatocellular carcinoma (HCC). Methods: From January 2015 to December 2022, forty-eight patients with unresectable HCC underwent single or two therapeutic sessions of HIFU under general anesthesia. Ten patients with liver metastasis from colon cancer and three patients with liver metastasis from stomach cancer were included. We used HIFU, ultrasound-guided extracorporeal system (HIFU Technology Company, Chongqing, China). Thirty-three patients received transarterial embolization before HIFU. Thirteen patients were treated with chemotherapy before HIFU. Technical effectiveness per patient and per masses was assessed according to clinical findings and MR imaging at follow-up. Complications were also recorded. Results: We treated total 78 tumors in 48 patients. The tumor size ranged from 1.3 cm to 12 cm in diameter. Small (< 3 cm), intermediate (3-5 cm) and large tumors (> 5 cm) are 44, 24 and 10 patients, respectively. Average procedure time was 4 hours 10 minutes with 68 minutes treatment time. We made the artificial pleural effusion to get treatment field in 25 patients. Mean follow-up period was 52 weeks. For the technical effectiveness per patient as follows: complete ablation with no evidence of recurrence on follow up in 18%, apparent complete ablation of target mass with progression of new lesions on follow up in 29%, recurrence after apparent complete ablation in 26%, and incomplete ablation at 2 week follow up in 27%. Average post-procedure hospital day was 5.4 days. No severe complication except mild right upper quadrant pain was observed after treatment. Conclusions: HIFU is an effective and safe treatment option for local image-guided tumor ablation in patients with unresectable HCC. Although further study is necessary, these results show that HIFU may be helpful in treating unresectable HCC. Research Sponsor: None.

Efficacy and safety of a combination of sintilimab, bevacizumab plus gemcitabine, and albumin-bound paclitaxel for initially unresectable gallbladder carcinoma: A prospective, single-arm phase II study. First Author: Miao Wang, Liver Surgery Department, Shanghai Cancer Center, Shanghai, China

Background: Immune checkpoint inhibitors plus chemotherapy had demonstrated important therapeutic advantages in biliary tract cancers (TOP-AZ and Keynote-966). At present the data of gallbladder carcinoma (GBC) is in blank condition almost, and the effectiveness remains to be improved. Further, the addition of bevacizumab to PD-1 inhibitors has improved the clinical results in carcinomas, such as hepatocellular carcinoma, for which therapeutic options have been limited. This study intended to explore the safety and efficacy of sintilimab combined bevacizumab with chemotherapy in the first-line treatment of initially unresectable GBC. Methods: The study was an ongoing open-label, single-arm, phase II trial (Clinical Trial ID: NCT05757336), which consisted of 2 parts: safety-run-in part, where pts received sintilimab (200mg/kg, iv, Q3W) + baevacizumab (7.5mg/kg, iv, Q3W) + gemcitabine (1000mg/m\textsuperscript{2}, iv, d1, Q2W) and albumin-bound-paclitaxel (125mg/m\textsuperscript{2}, iv, d1, Q3W), followed by experimental part to evaluate the efficacy and safety of this strategy. The primary endpoint was safety and objective response rate (ORR) assessed by RECIST v1.1. Secondary objectives included disease control rate (DCR), progression free survival (PFS) and overall survival (OS).

Results: No DLT was reported at safety-run-in part. Up to the end of Sept 2023, 15 patients were enrolled with a median age of 60.4 years (range 46-75), 26.7% were male. Median follow-up time was 3.68 months. All patients completed at least one tumor response evaluation, confirmed ORR was 60.0% and DCR was 93.3%. Median PFS and OS was not reached yet. Grade 3 TRAEs occurred in 40.0% of patients (n=6), and the most common TRAEs (incidence>5%) among them were rash (20.0%), AST elevation (6.7%), fever (6.7%), platelet count decreased (6.7%), fatigue (6.7%), pneumonitis (6.7%).

Conclusions: The combination of sintilimab, bevacizumab and AG chemotherapy was tolerable and showed a promising ORR in initially unresectable GBC patients. This regimen could be a feasible and safe option for initially unresectable GBC, but this needs further validation. Clinical trial information: NCT05757336. Research Sponsor: None.

Understanding the efficacy of frontline therapies for hepatocellular carcioma through etiologic stratification. First Author: Maksym Goryachov, University of Colorado School of Medicine, Aurora, CO

Background: Despite significant advancements in recent years, hepatocellular carcinoma (HCC) treatment options remain limited for patients who progress on locoregional therapies. Given the high prevalence of genetic drivers in HCC, the use of targeted therapies has been explored to better understand whether the etiology of HCC influenced the efficacy of four common first-line FDA approved systemic therapy regimens. Methods: This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database from 1/1/2003 to 8/1/2021 with 3519 HCC patients who have received either atezolizumab-bevacizumab (AB), nivolumab, sorafenib, or lenvatinib as a first-line systemic therapy. Information on demographics (age, gender, sex race, ethnicity, ECOG, SES index), cancer stage, and treatment type was collected. In addition, comorbidities of hepatitis B, hepatitis C, alcohol use, diabetes, and obesity were collected as surrogates for disease etiology: viral hepatic disease, alcohol induced hepatic dysfunction or non-alcoholic fatty liver disease (NAFLD). Patients with missing data in any of the population stratifying variables were excluded. Overall survival (OS), Progression-free-survival (PFS) and time to treatment discontinuation (TTTD) were analyzed for each systemic therapy stratified by etiology as endpoints. Kaplan-Meier (KM) univariate analysis was performed along with the log-rank test for the primary outcome. Multivariate analysis (MVA) was conducted on all three endpoints via cox proportional hazard model to adjust for possible covariates in the patient population. Results: After exclusion criteria, 548 patients with complete data were included (AB N=124, Sorafenib N=324, Lenvatinib N=61, Nivolumab N=39) with variable etiologic presence (hepatitis B N=14, hepatitis C N=50, alcohol use N=41, diabetes N=50, Obesity N=44). When comparing patients across all recorded systemic therapies stratified by the etiologic variables, there was no statistically significant difference in OS, PFS, or TTTD. When stratified by presence of Hepatitis B, patients treated with atezolizumab-bevacizumab trended towards improved outcomes but did not reach statistical significance (P = 0.064). Other treatments showed mixed results in relation to specific etiologies, but no clear trend in efficacy emerged. Conclusions: This early retrospective study suggests that systemic therapy for HCC is not significantly impacted by factors associated with the etiology of disease, such as hepatitis C, alcohol use, and obesity. However, small population sizes and potential nonrandom covariate missingsness in this study may obscure effects. Future studies are needed to further elucidate this trend along with subpopulation effects of other systemic therapies. Research Sponsor: None.
Characterizing outcomes of ERBB2-amplified bile tract cancer. First Author: Daniel Aaron Fox, Baylor College of Medicine, Houston, TX

Background: A subset of biliary tract cancers (BTC) feature amplification (amp) of the human epidermal growth factor receptor 2 (ERBB2) gene. The prognostic role and treatment in these patients (pts) are poorly understood. This study aims to characterize the clinical outcomes and molecular profiles of ERBB2-ampl BTC. Methods: We conducted a retrospective analysis of clinical outcomes data and next-generation sequencing (NGS) at MD Anderson (MDA) and Fox Chase (FC) centers. Survival analysis was performed from 2009-2023 in pts with ERBB2-ampl BTC including all cases of genomic alterations (GA) in other genes. Progression-free survival (PFS) and overall survival (OS) were assessed by the log-rank test. Results: 80 pts (MDA) were identified with ERBB2-amp BTC with documented treatment and NGS data. Pts (Table) who received ERBB2-directed therapy (22.4% and 21.5% surgery (21.5% and 20.02%), local RT with or without RTX- ablation/Y90 (excluding surgical pts, 20.6 x 11.6 m, p = 0.001) had significantly longer OS. Median PFS (mPFS) without ERBB2-directed therapy for 1st, 2nd, and 3rd line systemic therapy was 4.1, 2.2, and 2.2 m, respectively. pts with ERBB2-directed therapy was 4.1 m, but that of gemcitabine (gem)-based plus trastuzumab (tt) and 5Fu-based plus tt was 7.8 and 3.8 m (p=0.018). The most common concurrent-CA at MDA, any co-amps (72.7%, 19.2 vs. 20.3 m, p=0.69) and TT3P inactivating mutation (70.4%, 16.4 vs. 14.9 m, p=0.89), had no OS association; 3rd most common co-CA: FGFR2 (46.4%), had a trend toward a better OS (19.2 vs. 14.3 m, p=0.089). FMI database showed ERBB2 amp in 3.2%, 5.4%, and 8.9% in intrahepatic cholangiocarcinoma (iCCA), extrahepatic CA, and gallbladder cancer. The most common co-CA included TP53, CDAK2A/B, and CCNE1. FGFR2 fusions (ICCA) were mutually exclusive with ERBB2 amp (0%, MDA/FMI), DH1 (CCA) with ERBB2 amp, 5.3% and 4.3% (MDA and FMI). Conclusions: ERBB2-amp BTC has shorter mPFS or mOS without ERBB2-directed therapy, surgery, or local therapy, suggesting clinical benefit from multi-disciplinary care and targeted therapy. Co-CA with ERBB2-amp did not demonstrate a significant association with survival outcomes. Research Sponsor: None.

Treatment outcomes and DNA co-occurring with ERBB2 amp.
OS all patients
16.1 m

PFS, shemo
1st line gem-based vs. 5Fu-based
4.2 vs. 4.1 m (p=0.70)
2nd line gem-based vs. 5Fu-based
3.0 vs 3.2 m (p=0.89)

MDA (80) DNA co- GA
KRES (11.4%), ATM (11.2%), other ERBB2 GA (9.1%) (7963)
TP53 (74.3%), CDAK2A (34%), CDAK2B (19.1%), TERT (19%), SMAD4 (12.4%), CDKN2A (15.9%), CDK12 (12.4%), ERBB2 amp (11.7%), KRES mutations (14.6%), TP53 (11.4%), FGFR2 amp (11.4%), CDAK2A/B (15.9%)

FM1 DNA co- GA
IgCA (12.85)
TP53 (85.3%), CDAK2A (37.3%), CDAK2B (21.3%), SMAD4 (20.5%), METAP loss (14.8%), FGFR2 fusion (14.7%), ABM10 (11.3%), and ERBB3 (10.7%)

Gallbladder (1857)
TP53 (85.9%), CDAK2A (30.4%), CDAK2B (31.4%), CHK2 (19.1%), SMAD4 (15%), CDK12 rearrangement (12.4%), METAP loss (11.5%)

Comparison of the treatment effect between lenvatinib and atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma in pathological–diagnosed metabolic dysfunction–associated steatotic liver disease. First Author: Hirokazu Takahashi, Liver Center, Saga University Hospital, Saga, Japan

Background: Metabolic dysfunction-associated steatotic liver disease (MADSL) is one of the leading etiologies of HCC. Recent evidence indicates that MADSL might affect the response to immune checkpoint inhibitors and multi-receptor tyrosine kinase inhibitors in the treatment for unresectable hepatocellular carcinoma (HCC), yet real-world data with accurate pathological diagnosis of MADSL has not been confirmed. Methods: Patients with unresectable HCC who had been pathologically diagnosed with MADSL by liver biopsy and/or hepatectomy and later received treatment with lenvatinib (LEN) or atezolizumab plus bevacizumab (ATZ/Bev) as first-line systemic treatment for HCC were included. Outcomes of treatment with LEN or ATZ/Bev were compared. Results: A total of 48 patients who received LEN (n=26) and ATZ/Bev (n=22) were included. Median time from pathological diagnosis to the initiation of treatment was not different (LEN 1.542 days, ATZ/Bev 1.260 days; p=0.48). The degree of steatosis, inflammation, ballooning hepatocytes and fibrosis did not differ between LEN and ATZ/Bev. At the initiation of treatment, BCLC stage, albumin–bilirubin grade, and Child–Pugh grade did not differ between LEN and ATZ/Bev. The overall response rate and disease control rate evaluated with modified RECIST criteria were not different between LEN and ATZ/Bev (26.1% and 77.2% for LEN, and 22.7% and 70.8% for ATZ/Bev). Median progression-free survival (PFS) was not different between LEN and ATZ/Bev (266 days vs 287 days, p=0.278). Median overall survival (OS) of LEN tended to be longer than that of ATZ/Bev (1364 days vs 663 days, p=0.081). The potential advantage of LEN in OS was statistically significant in the patients with Child-Pugh score = 5 (P=0.046). A total of 17 patients received both LEN and ATZ/Bev treatment and order of the treatment did not associate with PFS and OS. Conclusions: Outcomes of LEN and ATZ/Bev treatment for advanced HCC were not different in pathologically confirmed MADSL. Longer OS of LEN than ATZ/Bev was observed in the patients with relatively better liver function, suggesting that LEN might be a suitable first-line treatment for HCC with compensated liver function in the patients with pathologically confirmed MADSL. Research Sponsor: None.

Preliminary results of ALTER-H006: A phase II study of TQB2450 plus anlotinib as adjutant therapy in hepatocellular carcinoma (HCC) with high risk of recurrence after radical surgery. First Author: Xianhai Mao, Hunan Provincial People's Hospital, Changsha, China

Background: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality. Surgical resection remains as the mainstay of curative treatment, however, the recurrence rate after surgical resection could be high especially in patients with CNLC stage II or IIIa disease. Herein we evaluated the efficacy and safety of anlotinib (ANL) in patients with high-risk of recurrence after radical resection.

Methods: This prospective, multiple-center, single-arm phase II study (NCT05111366. Research Sponsor: Chia Tai Tian Qing Pharmaceutical group co. LTD (CTTQ). In this single-center, open-labeled, single-arm, phase II study, patients with advanced hepatocellular carcinoma who previously received systemic treatment. First Author: Takeshi Terashima, Department of Gastroenterology, Kanazawa University Hospital, Kanazawa, Japan

Background: Atezolizumab plus bevacizumab (AteBev) has been established as a standard of care for patients with unresected advanced hepatocellular carcinoma (HCC). Lenvatinib was once the first choice and remains a treatment option for such patients; however, no subsequent treatment to date has proven a similar level of efficacy. This study aimed to evaluate the efficacy of AteBev in patients with HCC previously treated with lenvatinib. Methods: In this single-center, open-labeled, single-arm, phase II study, patients with advanced hepatocellular carcinoma who had previously treated with lenvatinib were enrolled to receive 1,200 mg of atezolizumab and 15 mg/kg of bevacizumab intravenously every 3 weeks. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, response rate, tumor control rate, and frequency of adverse events. The threshold expected and expected PFS were 3 months and 6 months, respectively, at a one-sided significance level of 0.05, and statistical power of 80%. Based on these data, the number of patients required was estimated to be 26. Results: Among 29 patients enrolled between November 2020 and October 2022, 26 previously treated with lenvatinib were included in the primary efficacy analysis. Median PFS was 9.0 (90% confidence interval (CI), 5.10–14.24) months. Median overall survival was 17.25 (90% CI, 3.18–27.85) months, and response rate and tumor control rate were 34.6% and 69.2%, respectively. Severe adverse events were observed in six patients (23.1%), six patients (23.1%) discontinued treatment because of immune-related adverse events or treatment-refractory ascites, and 10 patients (38.5%) required the withdrawal of treatment mainly because of proteinuria. There were no treatment-related deaths. Conclusions: We believe that lenvatinib with lenvatinib had a comparable efficacy to that in patients with no prior treatment. It may therefore be a treatment option for patients with advanced HCC previously treated with lenvatinib. Clinical trial information: JRCT041200068. Research Sponsor: None.

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Lenvatinib plus hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma. First Author: Makoto Yamamoto, Department of Interventional Radiology, Kanazawa University Hospital, Kanazawa, Japan

Background: A recent phase II study demonstrated that combination therapy with lenvatinib and hepatic arterial infusion chemotherapy using cisplatin (Lenva+CDDP) had high anti-tumor effects for patients with advanced hepatocellular carcinoma (HCC) with no prior history of systemic chemotherapy; however, whether the efficacy of Lenva+CDDP is superior to lenvatinib monotherapy remains unclear. Methods: We retrospectively reviewed the medical records of patients with advanced HCC and a Child–Pugh score of 5, 6, or 7 who were treated with Lenva+CDDP or lenvatinib, and compared the efficacy between the treatments. Patients in both groups received a once daily dose of lenvatinib (8 mg or 12 mg according to their weight), and the Lenva+CDDP group also received 65 mg/m² of CDDP via the hepatic artery every 4 weeks. Treatment was repeated until tumor progression or unacceptable toxicity was observed. Results: A total of 140 patients (40 in the Lenva+CDDP group and 100 in the lenvatinib group) were included in this analysis. Patient backgrounds were comparable between the two groups, and 12 and 19 patients were previously treated with immunotherapy in the Lenva+CDDP group and lenvatinib group, respectively. The objective response rate and tumor control rate, assessed by RECIST ver1.1, in the Lenva+CDDP group were 67.5% and 100%, respectively, which was higher than in the lenvatinib group (17.0% and 87.0%, respectively). Median progression-free survival (PFS) and overall survival (OS) were 8.8 months and 19.6 months, respectively, in the Lenva+CDDP group, and 5.6 months and 20.3 months, respectively, in the lenvatinib group. Among patients who previously received immunotherapy, the median PFS, median OS, and 1-year survival rate were 9.7 months, not reached, and 87.5%, respectively, in the Lenva+CDDP group, and 4.7 months, 15.8 months, and 64.7%, respectively, in the lenvatinib group. Hematological toxicities were the main grade 3–4 adverse events (AEs) more frequently observed in the Lenva+CDDP group compared with the lenvatinib group. However, all grade 3–4 AEs were reversible, and there were no treatment-related deaths in either group. Conclusions: Lenva+CDDP demonstrated a better response and patient outcome than lenvatinib, and was well-tolerated in patients with advanced HCC. We are currently conducting a randomized controlled trial comparing the efficacy of these treatments. Research Sponsor: None.

Fruquintinib combined with sintilimab plus transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma: A single-arm phase II study. First Author: Guoliang Shao, Department of Interventional Radiology, Zhejiang Cancer Hospital, Hangzhou, China

Background: Tyrosine kinase inhibitor combined with immune checkpoint inhibitor has been reported a synergistic survival benefit in patients with unresectable hepatocellular carcinoma (uHCC). TACE induces tumor necrosis and tumor antigen release was believed to increase immune responses of anticancer immunotherapies. This study aimed to evaluate the safety and efficacy of fruquintinib combined with sintilimab plus TACE for uHCC. Methods: This study was a single-arm, open-label phase II exploratory clinical study (NCT05971199). Eligible patients were uHCC liver cancer stage (CNLC II) bil-ill-ill patients not candidates for surgical resection or ablation, or liver transplantation, at least one target lesion evaluable, ECOG performance status of 0–1, and Child-Pugh score ≤7. Enrolled patients would receive treatment with TACE (TACE was repeated on demand, but <5 times) followed by sintilimab 200 mg every 3 weeks and fruquintinib (5 mg QD, 2w on/1w off) until intolerable toxicity or disease progression. The primary endpoint was progression-free survival (PFS). The secondary endpoints included adverse events (AEs), overall survival (OS), objective response rate (ORR) and disease control rate (DCR) per mRECIST. Results: As of August 20, 2023, 15 enrolled patients with uHCC were treated. Mean follow-up time is 10.7 months. The median age was 58 years. At present, 10 patients were included for efficacy and safety analysis evaluation. Number of patients with CNLC stage IIb and Illa was 0 (0 %) and 15 (100 %), respectively. The median PFS and OS data are not yet mature. The ORR and DCR were 80% and 100% respectively based on mRECIST (1 CR; 10 %; 7 PR; 70 %; 2 SD; 20 %). The most common (≥10 %) TRAEs (≥Grade 3) were elevated glutamic oxaloacetic transaminase, hyperglycemia, proteinuria. No unexpected toxicity or treatment-related deaths occurred. Conclusions: Fruquintinib combined with sintilimab and TACE is a promising and tolerable therapeutic regimen for patients with CNLC Illa-Illa uHCC. This study is still ongoing and further follow-up is required to obtain final survival results. Clinical trial information: NCT05971199. Research Sponsor: HUTCHMED Limited.
Initial uptake of durvalumab with or without tremelimumab for advanced hepatocellular carcinoma in routine clinical practice. Preliminary results of the international DT-real study. First Author: Ciro Celsa, Department of Surgery and Cancer, Imperial College, Hammersmith Hospital, London, United Kingdom

Background: HIMALAYA trial showed that durvalumab plus tremelimumab (Single Tremelimumum Regular Interval Durvalumab; STRIDE) significantly improved overall survival (OS) and that durvalumab (DUR) was non-inferior compared to sorafenib in patients with hepatocellular carcinoma (HCC). However, third findings on this regime have not been described. Methods: In the context of a prospectively maintained database including 953 patients (pts) with unresectable HCC treated with immunotherapy, we analysed a subgroup of pts treated with STRIDE or DUR across 5 centers in USA, Asia and Europe. We assessed OS, progression-free survival (PFS), objective response rate (ORR) by RECIST 1.1 and overall response rate (ORR) by mRECIST, the outcomes of patients at high risk of recurrence. Results: Between February and May 2023, 59 pts initiated treatment with STRIDE or DUR (mean age 67.2 years, male sex 81.4%). 33 pts (55.9%) were treated in first-line (1L) and 26 (44.1%) in second- or further-line (>1L). STRIDE regime was administered in 24 patients (40.7%); 6 pts in 1L, 18 pts in >1L. Child-Pugh class A was in 32 pts (54.2%), being more common in pts treated with STRIDE than DUR (79.2% vs 37.1%, p=0.003). ECOC-GS was 0 in 35 pts (59.3%) and it was more common in pts treated with STRIDE than DUR (79.2% vs 47.0%, p=0.015). Outcomes are reported in Table. After a median follow-up of 3 months (95%CI 2.6-3.8), median OS was not reached and 6-month OS rate was 59.4%. In pts treated with STRIDE, median OS was not reached and 6-month OS rate was 55.8%, while median OS was 4.9 months (95% CI 2.3-4.9) for DUR. Median PFS was 2.5 months (95% CI 1.9-3.8) and ORR (evaluable in 43 pts, 72.9%) was 16.3% (95%CI 6.5-33.5%). Any grade TRAEs and grade 3-4 TRAEs were 42.4% (95%CI 27.4-62.5) and 10.2% (95% CI 7.3-22.1), respectively. TRAEs requiring systemic corticosteroid therapy occurred in 3 pts (5.1%). Conclusions: Preliminary observational data from DT-real confirm uptake of STRIDE and DUR across various lines of therapy, with encouraging efficacy and safety outcomes in routine practice. Research Sponsor: None.

503 Perioperative lenvatinib combined with tislelizumab plus transcatheter arterial chemoembolization in resectable hepatocellular carcinoma with high risk of recurrence: A prospective, single-arm, phase 2 trial. First Author: Jia-Yi Wu, Fujian Provincial Hospital, Fuzhou, China

Background: Early recurrence is common after surgery for hepatocellular carcinoma (HCC) and associated with poor prognosis. There is no standard of care neoadjuvant therapy. The combinations of lenvatinib, anti-PD-1 antibodies and transcatheter arterial chemoembolization (TACE) (triple therapy) has shown better trend in tumor response and survival outcomes on unresectable HCC. This study aims to explore the efficacy and safety of triple therapy in the neoadjuvant therapy of resectable HCC patients with high risk of recurrence. Methods: This prospective, single-arm, phase 2 trial (ChiCTR2100048249) enrolled patients with primary resectable HCC who had not received prior anti-tumor therapy. TACE will be performed once on Day 1. Tislelizumab (an anti-PD-1 antibody, one dose) will be intravenously given 5 days later and 3 weeks after the first TACE. Lenvatinib (bodyweight ≤ 60 kg, 12 mg; > 60 kg, 8 mg) orally daily was initiated within 7-10 days after TACE surgery. Treatment was performed 8 weeks after TACE surgery. After 4-8 weeks of surgery, patients continued to receive tislelizumab and lenvatinib for 6 months. Primary endpoint was relapse-free survival (RFS). Secondary endpoints were objective response rate (ORR) by mRERIST, major pathological reactions, R0 resection rates, overall survival, and adverse events (AE). Results: From April 2022 to June 2023, 29 patients (median age, 54 years) from ten Chinese hospitals were enrolled, all Child-Pugh A and ECOC GS 0, mostly males (79.3%) and HBV infection (93.1%). According to mRECIST, the ORR was 89.7% (26/29, CR 4, PR, 22), and the DCR was 96.7% (26/29). No grade 3 or above AE were observed. The most common AE were rash (4/29, 13.8%), fatigue (7/29, 23.2%), and nausea (4/29, 13.7%). 2 patients (2/29, 10.3%) had proteinuria. One patient had grade 3 anemia, and only 1 patient had grade 3 thrombocytopenia. Conclusions: The interim analysis of a single-arm, open-label, phase II study investigating the combination therapy of Albumin paclitaxel, Durvalumab and Lenvatinib (ALLEN regimen) is safe and shows promising efficacy in routine practice. HEPATOBILIARY CANCER 125s

504 The interim analysis of a single-arm, open-label, phase II study investigating ALLEN regimen (durvalumab plus albumin paclitaxel and lenvatinib) in patients with unresectable biliary tract cancers (BTCs). First Author: Zhifang Li, Department of Bio-therapeutic, The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China

Background: BTCs are a heterogeneous group of malignancies with a poor prognosis. Despite the improved outcome achieved by the addition of the anti-PD-L1 antibody durvalumab to standard chemotherapy, the benefits were modest and cannot satisfy the clinical demands adequately. This study aimed to evaluate the efficacy and safety of the combination therapy of Albumin paclitaxel, Durvalumab and Lenvatinib (ALLEN regimen) in unresectable BTCs. Methods: This single-arm, single-center, open-label, phase II study enrolled patients with locally advanced or metastatic BTCs. Eligible patients with ECOC score 0-2 were treated with ALLEN regimen. Durvalumab (1000mg IV, q3w) in combination with albumin paclitaxel (180-220 mg/m² IV q3w) and lenvatinib (8mg PO qd) were given regularly until disease progression. The primary endpoint was objective response rate (ORR) evaluated by investigators according to RECIST 1.1. The secondary endpoints were disease control rate (DCR), progression-free survival (PFS) and treatment-related adverse events (TRAEs). Results: From September 2021 to September 2023, fourteen patients were enrolled including three patients who failed to prior anti-PD-1 antibody treatment. The median follow-up was 6.8 months (95% CI 1.9, 10.9). The median age of the patients was 59.0 years, and male patients accounted for 35.7%. The ORR and DCR were 35.7% and 100%, respectively. The median PFS was 7.3 months (95% CI 4.9, 8.2). TRAEs of any grade occurred in 13 (92.9%) patients without grade 3 or higher. The most common TRAEs were alopecia (13/29, 79.2%), peripheral sensory neuropathy (10/14, 71.4%), decreased appetite and nausea (9/14, 63.6%), hypertension (7/14, 42.9%), rash (5/14, 35.7%), diarrhea (4/14, 28.6%) in TACE group. The 1 year DFS rate was 81.2% (95% CI: 70.8%-93.1%) in lenvatinib + TACE group, which was significantly higher than that of TACE group (58.3% [95% CI: 46.8%-72.7%], p = 0.0087; HR = 0.44 [95% CI: 0.23-0.83}). The median DFS rate was not reached (95% CI: 28-NR) in lenvatinib + TACE group, and was 20.0 months (95% CI: 12.0-NR) in TACE group. Patients’ liver function after treatment with TACE + lenvatinib was better than that of TACE alone. Conclusions: The preliminary results of this study suggested that lenvatinib combination in TACE can significantly improve DFS compared with TACE alone in patients with HCC at high risk of recurrence after surgery. The toxicity of combined treatment was tolerable and manageable. The follow up is still ongoing to observe the long-term benefit of this treatment regimen. Research Sponsor: None.

505 Adjuvant TACE plus lenvatinib as compared with TACE alone in patients with hepatocellular carcinoma at high risk of recurrence after surgery: A prospective controlled study. First Author: Bin Zhang, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Hepatocellular carcinoma (HCC) remains the fourth leading cause of cancer deaths globally. The 5-year survival rate is still low in routine curative surgery for patients with resectable HCC in China. However, the high 5-year postoperative recurrence rate of about 40% to 70% had become the main negative factor affecting the long-term survival benefit. Although transarterial chemoembolization (TACE) can effectively reduce the recurrence rate and improve disease-free survival (DFS) and overall survival (OS), the outcomes of patients at high risk of recurrence are still not satisfactory. Thus, there is an urgent need for new adjuvant treatment regimen to further improve the survival outcomes. In this study, we compared the efficacy and safety of the lenvatinib plus TACE for adjuvant therapy for resectable HCC with highrisk of recurrence. Clinical trial information: ChiCTR2100048249. Research Sponsor: Natural Science Foundation of Fujian Province.
Phase 1 trial of navitoclax and sorafenib in patients with refractory solid tumors with a hepatocellular carcinoma expansion cohort. First Author: Adi K. Korman, Mayo Clinic, Rochester, MN

Background: Neoadjuvant use of immune checkpoint inhibitors (ICI) is feasible and achieves pathological responses in a subset of patients with hepatocellular carcinoma (HCC). However, it is not clear whether pathological response to ICI translates into long-term survival benefit. Methods: We analyzed patient-level data from 86 subjects recruited to 4 prospective phase II/III clinical trials of ICI prior to liver resection (LR) in 9 centers in the United States, Europe, and Asia and included a cohort of 22 patients (pts) receiving neoadjuvant ICI off trial. Radiological response was assessed with RECISTv1.1. Major (MPR) and complete pathological response (pCR) were considered as ≥70% and 100% non-viable tumor in the resected specimen, respectively. Pathological responses were correlated with radiologic overall response rates (ORR) and relapse-free survival (RFS). Results: Out of 109 pts treated between 2016/7 and 2002/3, 55 pts (50.5%) received a double ICI combination, 35 (32.1%) ICI monotherapy, and 19 (17.4%) an antiangiogenic/ICI combination. In 19 pts (17.4%) an adjuvant ICI course was administered for a median time of 5.5 months (interquartile range [IQR] 3.7-6.0). Most of pts were male (77.6%) with underlying viral chronic liver disease (68.2%), performance status 0 (83.5%), BCLC 0-A (55%), a median tumour diameter of 6.0 cm (IQR 3.9-9.9) without portal vein thrombosis (75.7%). After a median follow-up of 27.3 m (95% CI 21.5-33.0), 35 (32.1%) relapses and 14 (12.8%) deaths occurred. Radiologic ORR was 28.5% (n=31), with 3.7% complete responses (CR; n=4) and 24.8% partial responses (PR; n=27). Out of 100 pts evaluable for a pathological response, 33% achieved MPR and 19% pCR. MPR was more likely in pts who had achieved a radiologic PR or CR (26%) as compared to those who did not (14% < p < 0.001), however linear correlation suggested an imperfect correlation between ORR and MPR (R^2 0.43, p < 0.0001). Median RFS was 43.3m (95%CI, 27.5-93.6), while median overall survival was not reached (NR). mRFS was significantly improved in pts with MPR (NR vs 28.3m [95%CI, 15.6-50.4], HR 0.20 [95%CI, 0.05-0.82], p=0.013). Conclusions: This study is the first to qualify the role of MPR as a putative surrogate endpoint for recurrence-free survival in pts treated with neoadjuvant immunotherapy for HCC. Validation in larger phase III clinical trials is warranted. Research Sponsor: None.

Impact of baseline liver function on survival outcomes in patients with unresectable hepatocellular carcinoma (HCC) treated with camrelizumab + rivoceranib vs sorafenib: A post hoc analysis of study CARES-310. First Author: Arndt Vogel, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

Author: Arndt Vogel, Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

Background: CARES-310 study (NCT03754293) evaluated the combination of camrelizumab, an anti-PD-1 inhibitor, and rivoceranib, a highly selective VEGFR2-tyrosine kinase inhibitor, (cam + rivo) vs sorafenib (sora) for the treatment of uHCC. Cam + rivo significantly improved median overall survival (mOS) compared with sora (19.1 m vs 15.1 m; hazard ratio [HR] 0.57 [0.38, 0.89]; p = 0.01) and improved response outcomes (aORR, mPFS, DCR, and ORR) compared with sora. These results support cam + rivo as a potential new first-line treatment option for patients with uHCC regardless of baseline liver function. Clinical trial information: NCT03754293. Research Sponsor: Elevation Therapeutics, Jiangsu Hengrui Pharmaceuticals.

Impact of baseline ALBI grade and CP class on survival and other outcomes in Study CARES-310.

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Impact of baseline ALBI grade and CP class on survival and other outcomes in Study CARES-310.

Overall ITT Population

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Impact of baseline ALBI grade and CP class on survival and other outcomes in Study CARES-310.
Comparison of neoadjuvant treatment modalities for locally advanced intrahepatic cholangiocarcinoma (IHCC) is resection. Nonetheless, most patients (pts) are diagnosed at a more advanced stage. In this population, using neoadjuvant treatment—locoregional therapies, systemic chemotherapy, or a combination—may improve survival outcomes and downstream them to resectable. We present data comparing survival outcomes (median overall survival [mOS], median progression-free survival [mPFS]) and resection rate (RR) among pts with locally advanced IHCC who received chemotherapy (CT-only), Y90-therapy with chemotherapy (Y90+CT) or Y90-TARE alone (Y90-only) as neoadjuvant treatment. Methods: A retrospective chart review of all pts from October 2015 to December 2022 with biopsy-proven IHCC was completed. Exclusion criteria included ECOG ≥ 2, stage IV hepatic disease, and having received previous treatment for IHCC. We defined the Y90+CT arm as pts who received ≤ 4 cycles before Y90 or chemotherapy < 8 weeks after Y90. Statistical analysis was performed with Chi-square, Fisher’s Exact, and Kruskal-Wallis tests. Kaplan-Meier analysis was used for survival calculations and a Log-rank test to compare the arms. Survival is reported as median and 95% confidence interval [CI]. Results: A total of 56 pts were included: 23 pts in the CT-only arm, 15 in the Y90+CT arm, and 18 in the Y90-only arm. The median age at diagnosis was 69 years (IQR 59-74), and 54% were male. There was no statistically significant difference in age at diagnosis or sex between the three arms. RR was 1/23 (4%), 5/10 (50%), and 7/11 (64%) in the CT-only, Y90+CT, and Y90-only arms, respectively (CT-only vs. Y90+CT, p=0.05; CT-only vs. Y90-only, p=0.01); mOS and mPFS for the cohort were 16.3 months [15.3-17.3] and 7.4 months [6.8-8.0], respectively. The mOS and mPFS for the CT-only arm were 14.0 months [10.1-14.0], 24.3 months [23.3-25.3], and 24.3 months [23.0-25.6] for the CT-only, Y90+CT, and Y90-only arms, respectively (CT-only vs. Y90-only, p<0.01; CT-only vs. Y90-only, p<0.01). The mPFS were 3.5 months [1.1-5.9], 6.2 months [3.8-8.6], and 10.5 months [8.3-12.6], respectively (CT-only vs. Y90-only, p<0.01; Y90-only vs. Y90-only, p<0.02). Conclusions: In the neoadjuvant setting, including Y90 as a treatment modality may improve survival outcomes and resection rates compared to using chemotherapy alone. Further analysis will include running the Cox multivariate regression model to control for factors that may affect treatment selection in this population. Research Sponsor: None.

A phase II trial of induction systemic mFOLFRINOX followed by hepatic arterial infusion of fluorouridine and dexamethasone given concurrently with systemic mFOLFIRI as a first-line therapy in patients with resectable, locally advanced intrahepatic cholangiocarcinoma (HELIX-1). First Author: Skye C. Mayo, School of Medicine, Department of Surgery, Division of Surgical Oncology, Knight Cancer Institute, Oregon Health & Science University, Portland, OR Background: Most patients with intrahepatic cholangiocarcinoma (ICC) have unresectable or multifocal liver-dominant disease. Survival after first-line systemic therapy remains poor, with median progression-free (mPFS) and overall survival of 7.2 and 12.8 months, respectively. Hepatic arterial infusion (HAI) therapy with fluorouridine maximizes liver-specific treatment with minimal systemic toxicity and potentially offers improved disease control when combined with systemic therapy. Methods: HELIX-1 (NCT04251715) is an investigator-initiated, first-line, single-center, single-arm phase II clinical trial for patients with liver-dominant unresectable or multifocal ICC. The trial was designed with a patient safety run-in evaluating toxicity from the combined therapy. Pre-trial screening included laparoscopy, biopsies, and PET/CT. Eligible patients were treated with systemic mFOLFRINOX for 4 cycles in order to select those likely to benefit from HAI. Patients with disease control on restaging proceeded to HAI pump placement and treatment with HAI fluorouridine for 14 days followed by systemic mFOLFIRI on a 28-day cycle. The co-primary objectives were to assess safety of the combined therapeutic strategy and the disease control rate (DCR) at 6 months (RECDIST v1) at end of trial (EOT). Results: A total of n=5 patients with liver-only ICC enrolled in the trial and completed the entire study protocol. The median age was 60 years (range 42-66) with a dominant lesion size of 9.8cm (range 8.4-14.5). All patients had both right and left hemiliver involvement with a median of 9 intrahepatic tumors (range 1-15). No patients experienced grade 3 or 4 adverse events, or hepatic dysfunction leading to cessation of HAI therapy. The DCR at 6 months was 100%, with a mPFS of 18.2 months. All five patients achieved partial radiographic response (PR) while receiving HAI therapy, and remain alive with liver-only disease at a median of 18.4 months (range 12.7-20) after study enrollment. After continuing treatment with HAI and systemic mFOLFIRI beyond the EOT, two patients transitioned to HAI treatment only and then to biochemical and radiographic surveillance without therapy after demonstrating PR and CA19-9 normalization. Conclusions: Integration of HAI fluorouridine with mFOLFIRI following mFOLFRINOX induction for patients with liver-only advanced ICC is well-tolerated and demonstrates longer DCR in comparison to historical controls. The combined regimen minimized systemic toxicity and allowed a large proportion of patients to transition to liver-only HAI treatment with maintained disease control. Future directions include combining HAI with new first-line systemic regimens for patients with advanced ICC. Clinical trial information: NCT04251715. Research Sponsor: None.
Liver toxicity following reirradiation and multiple-target SBRT for primary hepatocellular carcinoma. First Author: Jacob Hall, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Stereotactic body radiation therapy (SBRT) is increasingly used to treat hepatocellular carcinoma (HCC), but its safety in the treatment of multiple synchronous or recurrent lesions is underreported. We aim to better characterize SBRT-related hepatic toxicity in this population. Methods: We conducted a retrospective analysis of patients with primary HCC who underwent SBRT for 2 or more synchronous or recurrent liver lesions. We collected patient characteristics and dosimetric data (mean liver dose, cumulative effective volume [Veff], cumulative volume of liver receiving 15Gy [V15Gy]), and cumulative planning target volume (PTV) along with liver-related toxicity (measured by albumin-bilirubin [ALBi] and Child-Pugh [CP] scores). We employed a linear mixed-effects model to assess the effect of multi-target SBRT on changes in ALBi. Results: There were 25 patients and 56 lesions with median follow-up of 29 months. Eleven patients had synchronous lesions and 14 had recurrent lesions treated with separate SBRT courses. Eight local failures occurred at a median of 8 months (range: 4 – 25 months) after SBRT. Among those receiving multiple SBRT courses, there were 7 lesions with overlap of V15Gy (median V15Gy overlap: 38.0 mL, range: 29.6 – 388.2 mL). There was no association between cumulative Veff, V15Gy, or PTV and change in ALBi. Four of 25 patients an increase of Child-Pugh score by ≥ 2 points, within 3 to 6 months after SBRT. Neither increase in CP nor ALBi were associated with cumulative Veff, V15Gy, and PTV. Comparing the groups that received SBRT in a single course versus multiple courses revealed no statistically significant differences in liver toxicity. Conclusions: LiverSBRT for multiple lesions in a single or in separate courses results in wior hepatocellular carcinoma (HCC) patients. Immuno-therapy combined with targeted drugs have been the first-line therapy for advanced HCC and shown good response rate in never-squamous situation. However, the effectiveness and safety of the combination treatment has not been reported in HCC patients. To address this, we conducted the present phase 2 clinical trial of neoadjuvant treatments using tislelizumab in combi- nation with lenvatinib for HCC patients. Methods: Patients with resectable HCC patients who had previously undergone curative treatment were enrolled. Enrolled patients were treated with 2 neoadjuvant cycles of a combination of tislelizumab 200mg intravenously every 3 weeks and lenvatinib 8mg every day (12mg for patients over 60kg) for 4 weeks. Hepatectomy was conducted in six weeks after enrollment. One month after surgery, adjuvant combination of tislelizumab and lenvatinib was started for at least one year or until disease progression or intolerance of adverse reactions. The primary objective of the trial is to evaluate one-year disease-free survival (DFS) rate, and secondary endpoints include objective response rate (ORR) as assessed by RECIST 1.1, major pathologic response (defined as over 90% tumor necrosis), and safety consider- ations. Results: Until Sep 30th, 2023, a total of 14 patients have been enrolled. All participants underwent the complete neoadjuvant therapy with a combination of tislelizumab and lenvatinib before proceeding to hepatectomy. Throughout the neo- adjuvant phase, 14.3% (2/14) of patients occurred adverse events below grade 3, with no severe adverse events occurring. The most common adverse events were fatigue (in 2 patients), hypertension (in 1 patient) and reduced appetite (in 1 patient). In 14 patients, 12 patients underwent R0 resection and 2 were waiting for hepatectomy. The average time from the initiation of the neoadjuvant therapy to hepatectomy was approximately 40.42 days. On the radiological front, one patient (8.3%) exhibited a partial response, while 11/12 (91.7%) displayed stable disease with 8 patients had tumor shrinkage. In terms of pathologic outcomes, 25% of patients (3/12) achieved a complete response, whereas the remaining patients showed varying degrees of pathologic response, ranging from 5% to 85%. Conclusions: In summary, the dual therapy of tislelizumab and lenvatinib demonstrates encouraging safety and effectiveness as a neoadjuvant in- tervention for patients with HCC. The long-term results of this combined treatment approach are eagerly anticipated. Clinical trial information: NCT04015143. Research Sponsor: None.

LIVER SUSTAINMENT AND REPERFORATION ARE A DISRUPTIVE FORCE IN THE EPIDERMIS AND CONVERGE WITH CYTOSKELETAL ORGANIZATION. First Author: Zhizhen Zhao, Division of Dermatology, University of Cincinnati College of Medicine, Cincinnati, OH

Background: Wound healing is a dynamic process comprising inflammation, proliferation, ECM remodeling, and reorganization. The reorganization of the epidermis is a key step in wound healing. Methods: To study the effect of dermal injury on epidermal reorganization, we used a skin scratch model in vivo (unilateral alleviation of the skin) to assess the epidermis. The skin was damaged by the laser in vivo, and the biopsy was taken 1 day and 3 days after injury. The scratch was treated with PBS (saline) alone or with PBS containing tazarotene, a retinoid, or a retinoid analog, 1 week before and after laser injury. Results: Compared to PBS, tazarotene or analog treatment induced an overall decrease in epidermal thickness, and their effects appeared at the third and early stage of wound healing. Scratch healing was enhanced by retinoids and analogs. Conclusions: Tazarotene enhanced the healing of skin in vivo, and its effects could be beneficial to patients with chronic wounds. Further studies are needed to explore the mechanism by which retinoids enhance skin repair.
Comparing resection and stereotactic body radiation therapy for hepatocellular carcinoma with macrovascular invasion. A propensity score matched study. First Author: Michael Yan, Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada

Background: Macrovascular invasion (MVI) in hepatocellular carcinoma (HCC) patients is a poor prognostic factor. Current guidelines endeavor systemic therapy for MVI. Local therapies present a potential for obliteration of MVI and improved survival. Surgery has been the standard local therapy at our institution, and stereotactic body radiation therapy (SBRT) has emerged as an alternative local therapy for this patient population.

Methods: In this retrospective study, one-to-one optimal pair propensity score matching was used to compare outcomes of HCC patients with MVI who underwent surgery or received SBRT. Matching was done based on sex, age, ECOG, cirrhosis presence, Child-Pugh class, number of tumours, tumour volume, alpha-fetoprotein level, ALBI score, Japanese Classification of portal vein invasion, and hepatic vein invasion. Overall survival was estimated using the Kaplan-Meier method and between group differences determined using the log-rank test. The cumulative incidence of recurrence, accounting for the competing risk of death, was compared using Gray’s test.

Results: Ninety of 193 patients were included after matching (45 patients in both the surgery and SBRT groups (Table). The SBRT group had a median OS of 15 months (95% CI: 10-28), while in the surgery group it was 24 months (95% CI: 11-81). Comparing the 12-, 36-, and 60-month overall survival (OS) rates between the SBRT group (57%, 33%, 15%) and the surgery group (58%, 37%, 34%), there was no statistically significant differences (p=0.18), the 5-year OS was double in the surgical resection group. The 12-, 36-, and 60-month cumulative incidence of HCC recurrence in the SBRT group (47%, 73%, 75%) was comparable to the surgery group (69%, 69%, 69%) (p=0.89).

Conclusions: Long-term survival is possible in patients with HCC and MVI in a substantial minority of patients with HCC and MVI treated with local therapies. There was no statistical difference in outcomes; however, surgical resection resulted in numerically longer survival outcomes compared to SBRT after propensity score adjustment. There is rationale for investigating both local therapies with systemic therapies in future clinical trials. Research Sponsor: None.

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Salvage hepatic artery infusion chemotherapy after first-line systemic failure in patients with unresectable cholangiocarcinoma. First Author: Niaz Nasar, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Unresectable intrahepatic cholangiocarcinoma (IHC) is associated with poor overall survival (OS). Prior studies have suggested improved outcomes with hepatic artery infusion chemotherapy (HAIC), with or without systemic (SYS) compared to SYS alone, but the role of HAIC continues to evolve. This study compares outcome of HAIC when used as first-line treatment compared to the use of advanced IHC.

Methods: In this retrospective review, 722 consecutive biopsy-proven, liver limited IHC were evaluated from 2000-2018. Patients undergoing upfront surgery or those with metastatic disease beyond regional lymph nodes were excluded. Overall survival (OS) was estimated using Kaplan-Meier methods. Cox regression model was used to examine the association of HAIC given at any time point with OS. To further dissect the timing of HAIC therapy (1st vs 2nd line) on OS, multi-state models using parametric Cox regression, as well as separate Cause-specific hazard model to intergrade the transition to 2nd line HAIC from the 1st line SYS state were used to estimate the mean survival time from diagnosis. Results: 336 patients eligible for HAIC were analyzed. 137 patients began treatment with 1st line HAIC (median age 63, 40%, male) and 199 patients received 1st line SYS (median age 64, 46%, male). Median time to first treatment initiation was 1.8 vs 1.2 months for 1st line HAIC and SYS, respectively. Median OS of all patients was 22 months (95% CI: 20-25 months), and HAIC given at any time was associated with reduced all-cause mortality by 34% (HR: 0.66, 95% CI: 0.52-0.84).

Multi-states analyses revealed that patients who received 1st line HAIC had a mean OS of 33 months from disease diagnosis. Patients who transitioned to 2nd line HAIC after 1st line SYS had a mean DS of 36 months from diagnosis, while those who failed 1st line SYS and continued 2nd line SYS had a mean DS of 22 months from diagnosis. Patients who received no further treatment after 1st line SYS had a mean OS of 9 months. Median OS from the start of 2nd line for patients who received 2nd line HAIC was 18 months and 6 months for patients who started 2nd line SYS therapy. The sites of progression of disease (POD) in different treatment groups has been described in the Table. Conclusions: HAIC treatment of unresectable liver-dominant IHC at any time was associated with reduced mortality by 34%. Mean OS in patients treated with 2nd line HAIC did not appear to be significantly different than those receiving HAIC as 1st line therapy and both appeared to be superior to 2nd line SYS. The survival benefits of HAIC appear to be maintained after failure of 1st line systemic chemotherapy. Research Sponsor: None.

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Safety and efficacy of external beam radiation therapy (EBRT) after Yttrium-90 (Y-90) radioembolization in hepatocellular carcinoma patients previously treated with yttrium-90 radioembolization. First Author: Karolakphoon Thonglert, University of Washington, Seattle, WA

Background: Data on the safety and efficacy of external beam radiation (EBRT) after Yttrium-90 (Y-90) radioembolization for hepatocellular carcinoma (HCC) is limited. We report our experience using EBRT to treat HCC patients who were previously treated with Y-90. Methods: We analyzed 31 HCC patients who received EBRT following Y-90 treatment. Eighteen were treated with photon therapy (40-50 Gy in 5 fractions), and thirteen with proton therapy (42-67.5 Gy in 15 fractions). Twenty-four patients underwent Y-90 segmentectomies, while seven received Y-90 lobar treatment. The median administered Y-90 activity was 44.4 mCi (range 8.3-114.4).

Results: Twenty-four patients (77.4%) were eligible for retreatment with EBRT. The administered Y-90 activity was comparable to the EBRT area, thirteen outside the EBRT area, and eight in both regions. The median tumor size was 3.8 cm (range 1.6-19.4). Twenty-seven patients had Child-Pugh class A, three had Child-Pugh class B, and one had Child-Pugh class C. The median follow-up was 21 months, the 2-year progression-free survival, and overall survival rates were 28%, and 43%, respectively. The 2-year cumulative incidence of local failure was 7%. CP2 progression was observed in five patients (16%). Three had Y-90 delivered outside the EBRT area and two within the EBRT area. Three patients had possible RILD-related deaths. Grade 3+ biliary complications occurred in three patients (10%): one biliary, one liver abscess, and one bile stricture which resulted in a possible treatment-related death. All three patients had received at least two prior Y-90 treatment overlapping with the area treated with EBRT and had tumors located near the porta hepatis.

Conclusions: EBRT for HCC patients previously treated with Y-90 is feasible and offers excellent local control. Hepatic function and biliary toxicities are potential complications and should be weighed against the clinical benefits. Research Sponsor: None.

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A decade of chemotherapy management in hepatocellular carcinoma: A single-center study in Latin America. First Author: Wagner Eduardo Cruz Diaz, National Institute of Neoplastic Diseases (INEN), Lima, Peru

Background: Hepatocellular carcinoma (HC) is the most common primary tumor of the liver and is a significant health problem worldwide with check-point inhibitors and oral multikinase inhibitors (TKI) as the first-line therapy for advanced diseases. While chemotherapy treatment may not be standardized in current clinical management guidelines, it remains the only available treatment option in numerous Latin American countries.

Methods: A retrospective review was carried out, in patients older than 18 years, between January 2011 and December 2020. 127 patients were analyzed and identified, they had received at least one course of chemotherapy at the Instituto Nacional de Enfermedades Neoplásicas in Lima, Peru. Results: The median age was 40 years, 40 female patients (31.5%) and 87 male patients (68.5%). Among the participants, 77 patients (60.62%) were diagnosed with hepatitis B 2 patients (1.57%) had hepatitis C virus infections, and 48 patients didn’t have viral hepatitis. 72 patients (91.13%) underwent antitretoviral treatment. Non-cirrhotic patients were 118 (92.91%) and 111 (87.4%) had a Child A score. Chemotherapy was administered as first-line treatment to 118 patients (92.91%), with 47.61% receiving 5-FU-based chemotherapy, 11.11% Adriamycin, and 8.7% Gemcitabine-based chemotherapy. A smaller subset, consisting of 8 individuals (6.29%), received sorafenib as their first-line treatment. The overall survival (OS) rates at 12, 36, and 60 months were 74.14%, 20.69%, and 1.72%, respectively. Regarding disease-free survival (DFS) rates at 12, 24, and 48 months were 28.89%, 6.67%, and 2.22%, respectively. Conclusions: In this updated data for advanced hepatocellular carcinoma, we observed a subset of patients with advanced HC achieved favorable outcomes, with a median OS of 20.37 months and a median DFS of 6.6 months. Antitretoviral treatment may not be standardized in current clinical management guidelines, it remains the only available treatment option in numerous Latin American countries. Research Sponsor: None.
Novel GPC3-targeting radiopharmaceutical for hepatocellular carcinoma. First Author: Fanching Lin, Rayzebio, Inc., San Diego, CA

Background: Glypican-3 (GPC3) is a membrane-anchored oncofetal protein whose expression is largely absent in normal tissues. Significant upregulation of GPC3 protein has been observed in approximately 75% of hepatocellular carcinomas (HCC), and is associated with poor prognosis. The differential expression of GPC3 between tumor and normal tissue provides an opportunity for targeted radiopharmacuetical therapy (RPT) to treat HCC, a leading cause for cancer-related deaths worldwide. Methods: RA88-2009 comprises a novel macrocyclic peptide binder to GPC3, a linker, and a chelator that can be complexed with different radionuclides. The affinity of peptide binders to GPC3 was determined by surface plasma resonance (SPR) and radioligand binding assays. Target-mediated cellular internalization was radioimaged measured at multiple time points. In vivo biodistribution, monotherapy and combination treatments with 177Lu or 225Ac were performed in HCC xenografts. Results: RA88-2009 showed high binding affinity (Kd=0.7 nM) to human GPC3, with comparable affinity to GPC3 of human, mouse, canine and monkey origins, and no binding to other GPC family members. Potent cellular binding was confirmed in GPC3+ HepG2 cells, and was not affected by isotope switching. RA88-2009 achieved efficient internalization upon binding, with 42% internalized by 20 minutes in HepG2 cells. Biodistribution study of 111Lu-RA88-2009 showed sustained tumor uptake and fast renal clearance, with minimal or no uptake in other normal tissues. Exquisite tumor-specific uptake was also demonstrated in orthotopic HCC tumors with no uptake in surrounding normal liver tissue. Therapeutically, significant and durable anti-tumor effect and survival benefit were achieved with 177Lu and 225Ac-labeled RA88-2009, as monotherapy or in combination with lenvatinib, in GPC3+ HCC xenografts. Conclusions: Preclinical in vitro and in vivo data demonstrate the potential of RA88-2009 as a theranostic agent for the treatment of patients with GPC3+ HCC. Research Sponsor: None.

Histopathologic and genomic profile characteristics of biliary cancers related to pancreaticobiliary maljunction. First Author: Shodai Toyohama, Chiba University Hospital, Chiba, Japan

Background: Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic duct and bile duct anatomic downstream is outside the duodenal wall, and is associated with a high rate of biliary cancer. It has been reported that TP53 and KRAS mutations are not found only in the cancerous area but also in the noncancerous area. However, there is no report of precise mapping of genetic mutations throughout the gallbladder and bile ducts. Methods: Ninety-seven patients (including 31 patients with biliary cancer) who underwent cholecystectomy and cholangiectomy for PBM between 1990 and 2023 at our hospital and affiliated hospitals were included in the study, and consent forms were obtained from 36 patients. The panel targeting 60 genes frequently identified in biliary tract cancer was created in-house and deep sequenced to compare with clinicopathological features. To date, we analyzed 4 patients with biliary tract cancer and 5 patients without it (with prophylactic resection). The same analysis was also performed on cancerous and noncancerous parts of patients of gallbladder cancer and cholangiocarcinoma without confounding abnormalities for comparison. Results: A total of 33 Samples (7 cancerous parts and 26 noncancerous parts) were examined for biliary tract cancer. We found a variety of genetic abnormalities, including driver mutations such as TP53, ARID2, and BRCA2, in 9 noncancerous areas including hyperplasia and normal bile duct mucosa. Some of these mutations were not shared with cancerous areas. On the other hand, in 46 samples from 5 patients who did not develop gallbladder cancer (prophylactic resection), Driver mutations were found in only 3 sites. Pathological findings of dysplasia/hyperplasia in these pathologic results were observed in 28 of the 46 sections. In addition, Driver mutations were rarely observed in noncancerous areas in patients with normal gallbladder or cholangiocarcinoma. Conclusions: Unlike conventional biliary tract cancers, the patients with PBM showed a great variety of genetic abnormalities in both cancerous and noncancerous areas. On the other hand, in patients of prophylactic resection without cancer, driver mutations were almost completely absent despite the presence of mucosal changes. We believe that these findings can develop better strategy for biliary cancers with PBM. Research Sponsor: None.
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Cost-utility analysis of sequential therapy with sorafenib followed by regorafenib versus single-line therapies in advanced hepatocellular carcinoma. 
First Author: Jamie Grossman, Bayer, Columbus, OH 
Background: Sorafenib is the only licensed second-line therapy available for patients with advanced hepatocellular carcinoma (HCC) that progress on first-line sorafenib in the UK. We evaluated the lifetime cost-effectiveness of a sequence of treatment with sorafenib followed by regorafenib (SOR-REG) compared with licensed single-line therapies for which there is no clear sequencing options available, including atezolizumab plus bevacizumab (ATEZO+BEV), which has become the standard of care in first-line treatment, as well as lenvatinib (LEN), followed by best supportive care (BSC). 
Methods: Assuming a UK National Health Service and Social Services perspective, we developed a probabilistic individual-level semi-Markov model with states reflecting progression-free survival, progression following first-line treatment, further progression following second-line treatment, and death. First-line overall survival (OS) and progression-free survival (PFS) were informed by fractional polynomials network meta-analysis of published trials. Individual patient data from a phase 3 trial (RESORCE) on sorafenib and BSC informed OS and PFS in the second-line setting. Costs and utilities were sourced from published studies. Cost-effectiveness was summarized using incremental net monetary benefit (INMB), which could be positive or negative depending on direction of expected benefit associated with SOR-REG, and cost-effectiveness acceptability curves at willingness-to-pay (WTP) thresholds. 
Results: We found 1000 probabilistic samples and 1000 patients were sufficient for convergence. Lifetime costs were highest with ATEZO+BEV ($80,963 [95% CI: $11,022, $97,369], followed by SOR-REG ($38,072 [$31,864, $43,420]) and LEN ($37,351 [$35,025, $39,580]). Quality-adjusted lifetimes (QALYs) were highest with ATEZO+BEV (1.027) [0.152, 1.239], followed by SOR-REG (0.942 [0.802, 1.057]) and LEN (0.755, [0.094, 1.092]). At a WTP threshold of £30,000 / QALY gained, SOR-REG had an INMB of £40,211 (95% CI £-2,099, £52,731) and £4,589 (-£8,044, £14,481) versus ATEZO+BEV and LEN, respectively. 
Conclusions: A sequence of SOR-REG for patients with advanced HCC is cost-effective at WTP thresholds of £30,000 / QALY gained due to lower lifetime costs and broadly comparable QALY gains with single-line ATEZO+BEV and LEN in the UK. Broader second-line treatment options are needed for patients receiving ATEZO+BEV and LEN as first-line therapies. Research Sponsor: Bayer Pharmaceuticals.

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Prognostic value of minimal residual disease profiling in resectable hepatocellular carcinoma. First Author: Jie Hu, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China 
Background: Detecting post-surgical residual disease is a critical clinical requirement in resectable hepatocellular carcinoma (HCC). Previous studies focused on specific genomic regions have indicated that ctDNA holds promise as a tool for prognostic assessment. Nevertheless, these methods exhibited limited sensitivity and failed to meet the minimal residual disease (MRD) threshold. Here we report the prognostic value of MRD profiling in HCC patients who have undergone hepatectomy. 
Methods: This retrospective study involved 88 HCC patients who underwent surgical resection in China, from January to May in 2016. During surgery, tumor and normal tissue specimens were collected. Plasma samples were obtained 7 days post-surgery. PredicineBEACON, a baseline tissue- or blood-informed MRD assay, was used for MRD profiling. This entailed identifying tumor-specific mutations through whole exon sequencing of tissue samples. Subsequently, a personalized MRD panel, selecting up to 50 mutations via bioinformatics pipelines merged with a fixed panel featuring 500 tumor actionable hotspots, was created for each patient. To detect MRD in post-surgery plasma samples, we employed ultra-deep sequencing at a coverage of 100,000x, utilizing the designed panel. 
Results: In the cohort of 88 patients, the distribution based on Barcelona Clinic Liver Cancer (BCLC) staging was as follows: 79.5% stage A (N=70), 12.5% stage B (N=11), and 8.0% stage C (N=7). The MRD assay identified 36 patients as MRD+ and 52 patients as MRD−. We observed significant correlations between MRD status and both relapse-free survival (RFS) and overall survival (OS). For MRD+ patients, the median RFS was 17.1 months, while it was not reached for MRD− patients (p=0.0013). Likewise, the median OS of MRD+ patients was 52.9 months, whereas it was 23.1 months for MRD− patients (p=0.001). 
Conclusions: This study demonstrated the clinical utility of ctDNA MRD assay in patients with resectable HCC. The utility of the MRD assay in other indications warrants further investigation. 

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Genomic characterization of cholangiocarcinoma with autoimmune etiologies. First Author: Xin Wang, Princess Margaret Cancer Centre, Toronto, ON, Canada 
Background: Chronic inflammation from autoimmune conditions is a well-recognized risk factor for cholangiocarcinoma in the Western world. Cholangiocarcinomas in the setting of autoimmune diseases are generally considered to arise due to an autoimmune response to the biliary epithelium, their biology is adequately understood, and the risks and benefits of immunotherapy approaches in this population are unknown. We describe the clinical and genomic characteristics of a cohort of cholangiocarcinoma patients with autoimmune etiologies. 
Methods: In a prospective cohort of 43 patients with mismatch repair proficient cholangiocarcinoma, we collected tumor and normal tissue specimens. Patients were divided into two groups: one with a history of autoimmune disease (Autoimmune+), and another with no history of autoimmune disease. ctDNA was collected from all patients 7 days after surgery. Furthermore, the assessment of post-surgical MRD status provided valuable prognostic insights into both patient survival and the risk of disease relapse. 
Results: Of the 246 patients, 69 (28.0%) were treated with Ate/Bev for more than one year. The long-term treatment group showed better Eastern Cooperative Oncology Group performance status, liver function, and lower residual hepatic tumor burden at baseline, compared to the group treated for less than one year. Additionally, treatment-related adverse events (AEs), and changes in liver function were evaluated. 
Conclusions: The MRD assay identified 36 patients as MRD+ and 52 patients as MRD−. We observed significant correlations between MRD status and both relapse-free survival (RFS) and overall survival (OS). For MRD+ patients, the median RFS was 17.1 months, while it was not reached for MRD− patients (p=0.0013). Likewise, the median OS of MRD+ patients was 52.9 months, whereas it was 23.1 months for MRD− patients (p=0.001). 
Conclusions: This study demonstrated the clinical utility of ctDNA MRD assay in patients with resectable HCC. The utility of the MRD assay in other indications warrants further investigation. 

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Clinical characteristics of patients with advanced hepatocellular carcinoma who received long-term treatment with atezolizumab and bevacizumab for more than one year. First Author: Youngun Kim, CHA University School of Medicine, Seongnam, South Korea 
Background: Atezolizumab plus bevacizumab (Ate/Bev) has become the standard of care for patients with advanced hepatocellular carcinoma (HCC). However, studies on patients receiving long-term treatment with Ate/Bev are still lacking. In this study, we evaluated the clinical characteristics and impacts on patients receiving Ate/Bev treatment for more than one year. 
Methods: We prospectively enrolled 246 patients with unresectable HCC who received Ate/Bev treatment at the Chonbuk National University Hospital (CBN) between May 2018 and June 2019. Inclusion criteria for these analyses were performed between patients treated with Ate/Bev for more than one year and those treated for less than one year. Additionally, treatment-related adverse events (AEs), and changes in liver function were evaluated. 
Results: Of the 246 patients, 69 (28.0%) were treated with Ate/Bev for more than one year. The long-term treatment group showed better Eastern Cooperative Oncology Group performance status, liver function, and lower residual hepatic tumor burden at baseline, compared to the group treated for less than one year. Furthermore, the long-term treatment group had a higher incidence of atezolizumab-related thyroid dysfunction (30.4% vs. 10.7%, p < 0.001), dermatologic toxicity (30.4% vs. 14.1%, p < 0.001), and bevacizumab-related hypertension (45.3% vs. 22.6%, p = 0.002) and proteinuria (68.1% vs. 39.0%, p = 0.001), compared to the less than one-year treatment group. The median time to onset of thyroid dysfunction and dermatologic toxicity after Ate/Bev treatment was 2.8 months and 3.3 months, respectively, while the median time to onset of hypertension and proteinuria was 4.2 months and 6.6 months, respectively. In the long-term treatment group, 39 patients (43.5%) showed an increase in Child-Pugh score, 20 (29.0%) had an increase in Child-Pugh grade during Ate/Bev treatment. 
Conclusions: The Ate/Bev long-term treatment group had better performance status, liver function, and a lower residual hepatic tumor burden at baseline, compared to the group treated for less than one year. Furthermore, the long-term treatment group had a higher incidence of atezolizumab-related thyroid dysfunction (30.4% vs. 10.7%, p < 0.001), dermatologic toxicity (30.4% vs. 14.1%, p < 0.001), and bevacizumab-related hypertension (45.3% vs. 22.6%, p = 0.002) and proteinuria (68.1% vs. 39.0%, p = 0.001), compared to the less than one-year treatment group. The median time to onset of thyroid dysfunction and dermatologic toxicity after Ate/Bev treatment was 2.8 months and 3.3 months, respectively, while the median time to onset of hypertension and proteinuria was 4.2 months and 6.6 months, respectively. In the long-term treatment group, 39 patients (43.5%) showed an increase in Child-Pugh score, 20 (29.0%) had an increase in Child-Pugh grade during Ate/Bev treatment. 
Conclusions: The Ate/Bev long-term treatment group had better performance status, liver function, and a lower residual hepatic tumor burden at baseline. Atezolizumab plus bevacizumab adverse events occurred mostly early in the course of treatment, whereas bevacizumab-related adverse events occurred relatively later. In addition, a fraction of patients experienced deterioration of liver function during the long-term Ate/Bev treatment. Research Sponsor: None. 

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534   Poster Session

Molecular predictors of response to first-line systemic therapies in advanced hepatocellular carcinoma. First Author: Jeremy Chang, University of California, San Diego, La Jolla, CA

Background: With numerous advances in systemic therapy for advanced hepatocellular carcinoma (HCC) over the past several years, there are now multiple first-line treatment options which can be considered. These options include combination atezolizumab with bevacizumab (atezo/bev), programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) targeted agents, and oral multikinase inhibitor monotherapy. However, further understanding of which patients will respond to best to each regimen is emerging. Methods: We performed a single-center, retrospective study to determine the association between responses to first-line therapies in advanced hepatocellular carcinoma and previous molecular alterations. Patients received first-line therapy with either atezol/bev, PD-1/PD-L1 monotherapy, or oral multikinase inhibitor monotherapy with treatment responses determined by imaging. All patients underwent next-generation sequencing (NGS) with testing performed on peripheral blood or tumor tissue. Results: A total of 116 patients with advanced HCC were included in this study. For first-line therapies, 45 (38.8%) patients received atezo/bev, 41 (35.3%) received oral multikinase inhibitor monotherapy, and 30 (25.6%) received PD-1/PD-L1 monotherapy. There was no association between treatment responses and patient ethnicity, age, or undergoing chrysothol etiology for any regimen. However, when analyzing NGS results, atezo/bev patients with telomere reverse transcriptase (TERT) promoter alterations had significantly higher rates of disease progression (PD) compared those without TERT promoter alterations (91.7% vs 56.4%, P = 0.03). In addition, in the oral multikinase inhibitor monotherapy group, those with CTNNB1 alterations had significantly greater PD rates compared to patients without these alterations (66.7% vs 31%, P = 0.04). There were no significant correlations between molecular alterations and responses in the PD-1/PD-L1 monotherapy group (Table). Conclusions: In our study, advanced HCC patients who received first-line systemic therapies were found to have significant correlations between TERT promoter and CTNNB1 alterations and response to atezol/bev and oral multikinase inhibitor monotherapy, respectively. Given the widespread use of these regimens in the HCC treatment paradigm, additional studies are needed to confirm these findings and determine their impact on survival outcomes. Research Sponsor: None.

Molecular alterations and responses to first-line systemic therapies.

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536   Poster Session

Molecular differences with therapeutic implications in early-onset compared to average-onset cholangiocarcinoma. First Author: Thejus Jayakrishnan, Taussig Cancer Institute, Cleveland, OH

Background: Early-onset cholangiocarcinoma (eoCCA) is among early-onset cancers with the fastest rising rates, yet little is known about their molecular alterations. We sought to compare the molecular characteristics of eoCCA with average-onset CCA (aoCCA) with an age cut-off of 50 years, utilizing a real-world multiomics dataset. Methods: The study comprised patients whose tumors underwent molecular analysis at Caris Life Sciences (Phoenix, AZ) using whole exome and whole transcriptome analyses. Patients were defined as early-onset CCA if their age as eoCCA was defined as <50 years and aoCCA >50 years. Gene expression profiles were analyzed for transcriptional signatures predictive of immunotherapy response including the T-cell inflamed score (TIS) and interferon-gamma (IFG) score. P values (adjusted for multiple testing) were considered significant at false discovery rate (FDR) <0.05 for molecular comparisons and FDR <0.05 for Gene Set Enrichment Analysis (GSEA). Insurance claims data was used for survival comparison using Kaplan-Meier estimates. Results: The study included 5587 patients - 453 patients with eoCCA and 5134 with aoCCA (Table). Of targetable mutations (FGFR2, BH1, BH2, BRCA1, BRCA2), FGFR2 fusion was significantly more prevalent in eoCCA (15.7% vs 5.9% in aoCCA, FDR P <0.001). Rates trended higher in eoCCA for H+H tumors (4.1% vs 2.4%), and high tumor mutational burden (6.1% vs 5.1%) but not significantly different (FDR P=1). The score (Fold Change FC) 1.1, FDR =0.007 FDR =0.0001) and TIS (FC:17.3, FDR P=0.03) were significantly higher in aoCCA vs eoCCA. On GSEA, anagengiology was enriched in eoCCA (normalized enrichment score NES=1.51, FDR P=0.01) while IFG (NES=1.58, FDR P<0.06) and inflammatory response (NES=1.46, FDR P=0.18) were enriched in aoCCA. Median OS was longer in eoCCA (16.5 vs 13 months, Hazard Ratio (HR) 0.69, 95% CI 0.78-0.95, P=0.004). Among patients treated with immunotherapy, median OS was longer in patients with eoCCA (19.2 months, n=19) vs aoCCA (7.5 months, n=150) - HR 0.52, 95% CI 0.28-0.94, p<0.03. No survival difference was identified in patients on chemotherapy (HR 0.91, 95% CI 0.76-1.08, P=0.28).

Conclusions: In the largest age-stratified analysis of molecular characteristics of CCA, we identified crucial differences, including higher prevalence of FGFR2 fusions and significant differences in immunotherapy-related markers, angiogenesis enrichment, and inflammatory response. Patients with eoCCA had better outcomes than those on chemotherapy even though immune-related-occe marks favored aoCCA. Our findings, especially higher FGFR2 fusion prevalence in eoCCA, underscore the need for NGS testing and the potential for age-tailored therapeutic strategies. Research Sponsor: None.

Characteristic | eoCCA | aoCCA |
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537 Poster Session

Association of FGFR2 structural alterations in intrahepatic cholangiocarcinomas with female gender and younger age. First Author: Zhihao Ian Hu, Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: FGFR2 fusions and other rearrangements are targetable alterations due to the advent of FGFR2 kinase domain inhibitors, and are considerably more common in intrahepatic cholangiocarcinomas (iCCA) than other cancer types. Understanding clinical factors associated with FGFR2 fusions and other rearrangements may guide precision oncology efforts. Prior studies indicate that FGFR2 alterations are more common in younger patients, but it remains unknown whether other demographics are specifically associated with FGFR2 structural alterations. Here, we reviewed the frequency of FGFR2 structural alterations in 8,898 iCCA patients from the AACR Genie and the Foundation Medicine databases. Methods: We reviewed the Foundation Medicine (n = 7,904) and AACR GENIE database (n=964) for intrahepatic cholangiocarcinomas. We identified iCCAs with FGFR2 structural alterations and mutations in other common driver genes and analyzed their distribution by age and sex. Results: FGFR2 structural alterations were more frequent in female (10.4%) compared to male (6.4%) patients across both cohorts. FGFR2 structural alterations had an association with an odds ratio of 2.5 (95% CI 1.6-3.7) and 1.7 (95% CI 2.0-6.7) with the female gender in the AACR GENIE and Foundation Medicine databases, respectively. The frequency of FGFR2 fusions/rearrangement was highest during reproductive years (up to age 40) and subsequently declined with age. This decline was greater in females than males. Mutations in other genes associated with iCCA including non-fusion FGFR2 alterations, and mutations in ARID1A, KRAS, and TP53 were not associated with gender or age. Conclusions: Our results show that FGFR2 structural alterations are significantly more enriched in younger female patients with iCCA. Clinical assessment of FGFR2 alterations should be prioritized in this patient population, and future clinical studies in this molecular subtype should ensure inclusive enrollment practices. Further research is warranted to determine if the pathogenesis of FGFR2 structural alterations are driven by female biology including the involvement of sex hormones and the potential impact on the development of acquired resistance to FGFR2 kinase inhibitors. Research Sponsor: None.

538 Poster Session

Prognostic effects of co-occurring TP53 and KRAS aberrations in patients with advanced biliary tract cancer. First Author: Taro Shibuki, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: In biliary tract cancer (BTC), TP53 is the most commonly altered gene and may co-occur with KRAS alteration. The presence of a co-alterations in of TP53 and KRAS is associated with poor prognosis in many cancers. In patients (pts) with advanced BTC, the prognostic implications of such co-alterations have not been fully investigated.

Methods: This is a pooled analysis of SCRUM-Japan GOZILA and MONSTAR-SCREEN-1 (Japan). Genomic profiling was conducted with Guardant360 for plasma in GOZILA, FoundationOne CDx for tissue and FoundationOne Liquid CDx for plasma in MONSTAR-SCREEN-1, and CARIS MI Profile for tissue in MONSTAR-SCREEN-2. Pts with advanced BTC receiving systemic therapy were included in this study. Results: Among 636 pts with advanced BTC, 85 had TP53/KRAS co-alteration, 293 had TP53, 44 had KRAS, and 214 had neither KRAS nor TP53 alteration (WT/WT). Tumors with TP53 alteration had significantly higher level of tumor mutation burden (TMB) compared to the other groups (3.8 mut/Mb for TP53/KRAS, 5.0 mut/Mb for TP53, 2.8 mut/Mb for KRAS, and 2.5 mut/Mb for WT/WT, respectively, P<0.001). In addition, the frequency of microsatellite instability-high (MSI-High) in the TP53/KRAS (11.0%) was significantly higher compared to the TP53 group (3.1%, P<0.05) and the WT/WT group (0.6%, P<0.001), respectively. The objective response rate of first-line therapy in the TP53/KRAS group (8.2%) was significantly lower than in the other groups (20.8% for TP53, 23.3% for KRAS, and 19.7% for WT/WT groups, P=0.035). There was no pts treated with durvalumab plus gemcitabine and cisplatin. Two pts with TP53/KRAS alteration and MSI-High received pembrolizumab monotherapy, and partial response was achieved with a progression-free survival of 9.4 and 22.0 months. The median overall survival (OS) for pts treated with first-line therapy of the TP53/KRAS, TP53, and WT/WT groups were 13.8 (95% confidence interval [CI], 11.5-15.5), 14.3 (95%CI, 9.7-27.9), 18.8 (95%CI, 16.1-21.7), respectively. Via multivariable analysis, we identified TP53/KRAS alteration (hazard ratio [HR] 2.14, 95% CI 1.43-3.22, P<0.001), number of detected variants (≥2) (HR 1.50, 95%CI 1.04-2.16, P=0.029), locally advanced (HR 1.72, 95% CI 1.05-2.83, P=0.033), and metastatic status (HR 1.78, 95% CI 1.39-2.28, P<0.001) as independent prognostic factors for shorter OS. Conclusions: Patients with advanced BTC with co-occurring TP53/KRAS alterations have worse prognosis. Interestingly, the presence of these co-alterations was associated with a higher likelihood of MSI-High phenotype. Research Sponsor: None.

539 Poster Session

Progression pattern and post-progression survival following atezolizumab and bevacizumab treatment in advanced hepatocellular carcinoma. First Author: Satoshi Kobayashi, Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan

Background: Although the combination of atezolizumab and bevacizumab (ATZ + BEV) is approved for 2 advanced hepatocellular carcinoma (HCC) strategies, for addressing treatment failure and prognostic factors of post-progression survival remain unestablished. Methods: We conducted a multicenter retrospective study to evaluate post-progression survival following ATZ + BEV treatment in patients with advanced HCC. We classified the patients into four groups: BCLC stage B with or without new intrahepatic lesions (BCLC-B1 and BCLC-B2, respectively) and BCLC stage C without or with new extrahepatic lesions (BCLC-C1 and BCLC-C2, respectively) at the time of progression. Results: Of the 204 patients who started ATZ + BEV treatment between October 2020 and September 2022, 110 showed disease progression, with 25, 8, 55, and 25 patients progressing in each respective group. Using the Tumor IMmune Estimation Resource (TIMER) deconvolution software to assess transcriptional dysregulation that occurs between the 2 groups. Immune deconvolution by transcriptional signatures differentiating PD-L1 high from PD-L1 low patients (pts), can be difficult to identify predictive biomarkers for guiding treatment. We hypothesize that genomic predictors of sensitivity to chemotherapy and immunotherapy in the CCA cohort of The Cancer Genome Atlas (TCGA-CHOL). We divided the pts (n=36) into 2 groups based on PD-L1 expression. Differential expression analysis, using Limma was utilized for Gene Set Enrichment Analysis (GSEA), to assess the predicted function of transcriptional dysregulation that occurs between the 2 groups. Immune deconvolution by using the Tumor Immunome Estimation Resource (TIMER) deconvolution software to assess differences in immune infiltration and resulting scores from this analysis were used to assess how immune cell population estimates correlated with immune factors, like PD-L1 expression, including PD-L1 and B Cells (R=0.42, p<0.009), and CD8+ and myeloid dendritic cells (n=3348, p=0.04). We noted significant correlations between immune cells deconvolution scores: CD4+ and CD8+ T-Cell (R=-0.35, p=0.02), CD8+ and neutrophils (R=0.42, p<0.009), and CD8+ and myeloid dendritic cells (R=0.48, p<0.002). Significant differences in immune deconvolution scores of CD8+ T Cells, macrophages, neutrophils were noted between PD-L1 high and low pts. Conclusions: PD-L1 high pts with CCA exhibit expected differential enrichment of immune signatures. Notably, we report for the first time that CCA PD-L1 low patients (n=25) if PD-L1 expression, assessed using TIMER revealed several significant correlations between immune cell deconvolution scores: CD4+ and CD8+ T-Cell (R=-0.35, p=0.02), CD8+ and neutrophils (R=0.42, p<0.009), and CD8+ and myeloid dendritic cells (R=0.48, p<0.002).
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Incidence and prognostic value of actionable mutations in early-stage resectable cholangiocarcinoma. First Author: Bailey Morgan Oppat, Emory University, Atlanta, GA

Background: Targeted therapy for actionable mutations in advanced cholangiocarcinoma (CCA) has revolutionized second and third-line treatment algorithms. Their application in early stage disease is not defined. The incidence and prognostic value of actionable mutations in pts with early stage resected disease is not known. Methods: The Cholangiocarcinoma Foundation and Citizens (a wholly owned subsidiary of Invitae Corporation) collaboratively launched a registry platform that prospectively consents pts and collects comprehensive medical records. Presently, de-identified data includes clinical characteris-tics, molecular testing, interventions, and outcomes have been extracted and standardized for research use on 400 pts. The data is longitudinal with regularly planned updates. We identified pts who underwent resection of non-metastatic disease and underwent genetic testing. Actionable mutations recorded included FGFR2 fusion/rearrangement, IDH1 mutation, HER2 amplification, BRAF mutation, MSI-high, and TMB-high. Primary outcome was recurrence-free survival (RFS). Results: Of 400 pts, 137 underwent resection for CCA. When compared to pts with advanced disease, those who underwent resection had a similar frequency of genetic testing and presence of actionable mutations: 94.3% (n=248) vs 83.9% (n=115) and 38.7% (n=96) vs. 33.0% (n=38), respectively. When considering pts with non-metastatic, resected disease who underwent molecular testing (n=104), the mean age was 59.2 years, 66 (63.5%) were females, and 60 (57.7%) had intrahepatic cholangiocarcinoma (iCCA), 42 (40.4%) had extrahepatic disease, and 2 (1.9%) were not otherwise specified. The majority received molecular testing before or at the time of surgery (n=89, 85.6%). Of pts with non-metastatic resectable disease who received genetic testing, 34 pts (32.7%) had actionable mutations: FGFR2: n=7 (6.7%), IDH1: n=16 (15.4%), HER2: n=5 (4.8%), BRAF: n=0 (0%), MSI-high: n=3 (2.9%), TMB-high: n=0 (0%). FGFR2 fusion/rearrangement and IDH1 mutations were only identified in iCCA. Pts with an FGFR2 fusion/rearrangement were younger (49.9 vs 59.8 yrs; p=0.03) and all were female. Although not statistically significant, the presence of an FGFR2 fusion/rearrangement was associated with nearly a doubling of RFS (32.0 vs 17.3 mos; p=0.19) for patients with iCCA. Conclusions: In this highly selected cohort of pts with resected, early stage, non-metastatic CCA, the majority underwent molecular profiling before or at the time of surgery. As expected, FGFR2 fusion/rearrangement and IDH1 mutations were only present in iCCA. An FGFR2 fusion/rearrangement was seen in young, female pts and may have a favorable prognostic value as suggested by a trend in increased RFS. Clinical trials are needed to assess the value of administering targeted therapy to this patient population in the adjuvant or neoadjuvant setting. Research Sponsor: Abraham J. & Phyllis Katz Foundation.

Des-gamma-carboxy prothrombin (DCP) as a biomarker for treatment response in hepatocellular carcinoma. First Author: Elizabeth Conner, University of California, San Diego, San Diego, CA

Background: Causes of variable disease response to first-line treatment with atezolizumab/bevacizumab (atezo/bev) in hepatocellular carcinoma (HCC) patients resistant to sorafenib are unclear. Measuring tumor markers throughout the treatment efficacy cycle helps identify variables of clinical suspicion for early disease progression. The role of des-gamma-carboxy prothrombin (DCP) is not well established in Hepatitis B Virus (HBV) non-endemic areas. This study aimed to investigate DCP as a predictive biomarker of atezo/bev treatment response in HCC patients. Methods: This single-center retrospective analysis evaluated DCP and radiographic response in HCC patients who received atezo/bev in the first-line setting. DCP was measured at the time of best response evaluation and compared to day 1 of atezo/bev initiation. Elevated DCP was defined by >7.5 mg/mL. DCP response was defined as a decrease of >50% at response assessment compared with baseline. Treatment response was evaluated based on imaging modalities including computed tomography and/or magnetic resonance imaging. Objective response rate (ORR) was defined as the percentage of patients with complete response (CR) and partial response (PR). Disease control rate (DCR) was defined as the percentage of patients with CR, PR, and stable disease (SD). No Response (NR) was defined as the percentage of patients with SD and PD. Comparisons of treatment effects were performed using two-tailed Fisher Exact Probability Test. Results: A total of 53 HCC patients treated with atezo/bev as first-line therapy were included. The best treatment responses according to radiographic evaluation were as follows: CR 3.8%, PR 22.6%, SD 52.8%, and PD 20.8%, respectively. Patients with DCP response had ORR of 69% (odds ratio, 15.5; 95% CI, 3.50-70.9; P= 0002) and DCR of 100% (P=0.047). Patients with >50% increase in DCP at response assessment compared to day 1 of one of two treatment of ORR of 4.2% and NR of 95% (P=0.0035). On day of one treatment, 70% of pts had an elevated DCP. There was no difference between elevated DCP vs non-elevated DCP on day one of treatment and ORR. Conclusions: This study found that DCP has utility in predicting response to atezo/bev for HCC patients in HBV non-endemic areas. Further studies are needed to confirm findings and evaluate therapeutic implications of DCP in HBV non-endemic areas. Research Sponsor: None.

Survival impact of homologous recombination deficiency in veterans with cholangiocarcinoma including mutational exclusivity with pathogenic KRAS and EGFR mutations. First Author: Colin P Bergstrom, Stanford University Medical Center, Stanford, CA

Background: Cholangiocarcinoma (CCA) has poor prognosis and limited treatment options. The US Veteran Health Administration’s (VHA) National Precision Oncology Program (NPONP) was established to characterize pathogenic drivers across the integrated VA network. Here, we summarize an important subgroup of CCA with homologous recombination deficiency (HRD) and its impact on overall survival (OS). Methods: Next-generation sequencing (NGS) was performed using FoundationOne CDx Analysis (Foundation Medicine, Cambridge, MA). Variants were prioritized for clinical relevance and were subjected to immunohistochemistry and/or FISH analysis. Statistical analysis was performed using Chi-squared test for concurrent gene enrichment and log-rank Kaplan-Meier analysis. Results: 483 CCA samples underwent tissue NGS as standard of care. Pathogenic variants in HRD genes included ARID1A (15.5%, n=75), BAP1 (9.5%, n=46), ATM (2.7%, n=13), PALB2 (2.3%, n=11) and BRCA2 (2.0%, n=10), representing 31.7% (n=153) of the population. HRD mutations were found in similar proportions of localized (31.8%) and metastatic (31.5%) clinical presentations at diagnosis. OS was not significantly different between CCA with HRD mutations (12.3 mo WT vs 13.8 months with HRD MT, p=0.64). KRAS MT (n=77, 15.9% of population) did not impact OS (WT 13.2 mo v. MT 13.1 mo) including subgroup analysis stratified by HRD status. There was increased frequency in KRAS MT with HRD WT 18.5% versus HRD MT 10.4% (p<0.03). Additionally, there was increased frequency in TP53 MT with HRD WT 54.8% versus HRD MT 28.1% (p<0.0001). TP53 MT (n=24, 46.3% of population) conferred worse OS (WT 13.0 mos v. WT 6.6 mos) including subgroup analysis stratified by HRD status. Subgroup analysis of TP53 MT had worsened OS with concurrent HRD MT (n=39, 4.1 mo) v. HRD WT (n=158, 9.0 mo; p<0.04). Conclusions: Across a diverse integrated healthcare system of Veterans, mutations associated with HRD were found to be common, however, not prognostic in OS across a diverse patient population of CCA. Further work is needed to characterize concurrent gene signatures of HRD, loss in heterozygosity of HRD, and platinum exposure to further define the patient population of CCA. Further work is needed to clarify exposure to platinum containing chemotherapy. TP53 MT CCA remains a critical unmet need that drives worsened outcomes including here in patients with mutations in HRD. Future analysis should consider mutation signatures of HRD, loss in heterozygosity of HRD, and platinum exposure to further define the subgroups of CCA with mutations in HRD. Research Sponsor: None.

Actionable molecular alterations in veterans with advanced cholangiocarcinoma. First Author: Ethan Samuel Lin, Department of Medicine, University of Wisconsin, Madison, WI

Background: Cholangiocarcinoma (CCA) requires integrated efforts to understand the heterogeneity of its tumor targets since the tumor markers that have been characterized thus far cannot explain the clinical suspicion for early disease progression. The role of des-gamma-carboxy prothrombin (DCP) is well established in Hepatitis B Virus (HBV) non-endemic areas. This study aimed to investigate DCP as a predictive biomarker of atezo/bev treatment response in HCC patients. Methods: This single-center retrospective analysis evaluated DCP and radiographic response in HCC patients who received atezo/bev in the first-line setting. DCP was measured at the time of best response evaluation and compared to day 1 of atezo/bev initiation. Elevated DCP was defined by >7.5 mg/mL. DCP response was defined as a decrease of >50% at response assessment compared with baseline. Treatment response was evaluated based on imaging modalities including computed tomography and/or magnetic resonance imaging. Objective response rate (ORR) was defined as the percentage of patients with complete response (CR) and partial response (PR). Disease control rate (DCR) was defined as the percentage of patients with CR, PR, and stable disease (SD). No Response (NR) was defined as the percentage of patients with SD and PD. Comparisons of treatment effects were performed using two-tailed Fisher Exact Probability Test. Results: A total of 53 HCC patients treated with atezo/bev as first-line therapy were included. The best treatment responses according to radiographic evaluation were as follows: CR 3.8%, PR 22.6%, SD 52.8%, and PD 20.8%, respectively. Patients with DCP response had ORR of 69% (odds ratio, 15.5; 95% CI, 3.50-70.9; P=0002) and DCR of 100% (P=0.047). Patients with >50% increase in DCP at response assessment compared to day 1 of one of two treatment of ORR of 4.2% and NR of 95% (P=0.0035). On day of one treatment, 70% of pts had an elevated DCP. There was no difference between elevated DCP vs non-elevated DCP on day one of treatment and ORR. Conclusions: This study found that DCP has utility in predicting response to atezo/bev for HCC patients in HBV non-endemic areas. Further studies are needed to confirm findings and evaluate therapeutic implications of DCP in HBV non-endemic areas. Research Sponsor: None.
Artificial intelligent (AI)-powered tumor microenvironment (TME) analysis to identify potential biomarkers for ICIs with or without bevacizumab in hepatocellular carcinoma (HCC). First Author: Hong Jae Cho, Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea

**Background:** While immunotherapies have been approved for use in HCC patients, there is a need for validated predictive biomarkers that correlate with treatment outcomes. We investigated whether AI-powered spatial analysis of non-cancerous cells within the TME can be potential biomarkers for ICIs with or without bevacizumab in advanced HCC.

**Methods:** Analysis of images of H&E-stained slides was conducted by an AI model, Lund SCOPE IO in pre-treatment tumor samples of 163 HCC patients treated with atezolizumab plus bevacizumab as first-line (n=82), or monotherapies of nivolumab or pembrolizumab as ± second-line (n=81) at CHA Bundang Medical Center or Samsung Medical Center. We analyzed the correlation between clinical outcomes after the treatment and AI-powered TME-related variables including TILs and endothelial cells, within intratumoral or stromal areas. Inflamed immune phenotype (IIP) was defined as cases exhibiting enrichment of intratumoral TILs. **Results:** Baseline characteristics, including Child-Pugh liver classification, Barcelona Clinic Liver Cancer stage, and hepatitis B virus, were well-balanced between treatment regimens. IIP was predictive of longer progression-free survival (PFS) of nivolumab or pembrolizumab monotherapy (median PFS 4.7 months for IIP vs. 2.2 months for non-IIP; hazard ratio (HR) 0.50; 95% confidence interval [CI] 0.25-0.99; p=0.042), but not PFS of atezolizumab plus bevacizumab (median PFS 6.8 months vs. 6.2 months; HR 0.92; 95% CI 0.50-1.69; p=0.762). PFS of atezolizumab plus bevacizumab was significantly longer in cases harboring intratumoral endothelial cell density in the highest quartile (median PFS 6.7 months for upper 25% vs. 39 months for lower 75%; HR 0.51; 95% CI 0.27-0.97; p=0.037), while there was no significant difference in PFS of pembrozulimab or nivolumab monotherapy (median PFS 2.3 months vs. 2.8 months; HR 1.02; 95% CI 0.59-1.77; p=0.935).

**Conclusions:** AI-powered TME analysis shows a predictive value of longer PFS with ICIs for patients with IIP, whereas intratumoral endothelial cell density is specifically associated with PFS of atezolizumab plus bevacizumab in advanced HCC. The latter finding may suggest efficacy of combined VEGFR and IC1 activity is dependent on the amount of baseline tumor vasculature. Research Sponsor: None.

Identification and characterization of immunogenic neoantigens in biliary cancer (BC) and pancreatic cancer (PC). First Author: Francesca Battaglin, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

**Background:** Recognition of tumor neoantigens by autologous T cells activates immune sur-}

**Results:** MSS/MSI-H rate was 1.8% in BC and 1.4% in PC. 117219 unique peptide:allele inter-

**Conclusions:** This study compared the mucosal microbiome from biliary tract among patients with CC, patients with CC, and HC. All three groups showed significantly different microbial profiles. In BC sample, the proportion of unclassified bacteria was high, and diversity and evenness were low, suggesting mucosal microbial dysbiosis. Further studies are needed to investigate the clinical implications of microbial dysbiosis in BC. Research Sponsor: None.

**Identification and characterization of immunogenic neoantigens in biliary cancer (BC) and pancreatic cancer (PC).** First Author: Francesca Battaglin, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

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Developing a comprehensive cell-free DNA (cfDNA) epigenetic signature (ep-Sig) with diagnostic and prognostic value in hepatocellular carcinoma (HCC). First Author: Ashish Manne, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: HCC is one of the deadliest tumors with poor outcomes often diagnosed in late stages. Current surveillance strategies (alpha-fetoprotein (AFP) plus ultrasound (USG)) for high-risk population (HRP) have poor sensitivity (SN) and reasonable specificity (SP) of 61% and 92%, respectively. Triple phase computed tomography (CT) imaging has good sensitivity and specificity (~ 90% for both) but the evidence does not support its use for routine surveillance. All these modalities do not have prognostic (survival) value. We attempted to develop a non-invasive, cfDNA-based tests to improve the diagnostic value of the current standard of care modalities (AFP and USG) and help in predicting the outcomes at diagnosis. We hypothesized that RNA and gene expression in HCC tissues is a surrogate for epigenome (DNA-methylation changes). Methods: We curated a 21-gene cfDNA ep-Sig from the literature with a proven prognostic value. Evidence suggests epigenetic changes in every gene of this panel affect HCC outcomes influencing clinicopathological characteristics (large tumor size, vascular invasion, advanced stage) or early post-operative recurrence, and survival. We compared RNA and gene expression of the genes in the ep-Sig between normal (NT) and HCC tissues using a web-based tool, TINOMPLot.com that uses the data from the Gene Expression Omnibus of the National Center for Biotechnology Information (NCBI-GEO) or Cancer Genome Atlas (TCGA). Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and The Genome-Tissue Expression (GTEx) repositories was used create this tool. It uses Mann-Whitney or Kruskal-Wallis tests to compute statistical significance. Results: RNA expression of all the genes from the ep-Sig was significantly higher in HCC than NT (1.133, p=5.84e-15). Gene expression was 19/21 genes was higher in HCC tissues (1.15, p=1.3e-08). The other 2 genes were not detected in the tested samples. Conclusions: Our ep-Sig which has a proven prognostic value and reliability was present in all HCC patients. This study is the first step in developing clinically useful blood-based test that can rework the current diagnostic and screening practices when used alongside AFP and USG. Research Sponsor: None.

555 Poster Session

Galeazzi-9 as a regulator of immune interactions in the tumor microenvironment and novel therapeutic target in biliary tract cancer. First Author: Emilie AK Warren, Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA

Background: While results of the TOPAZ-1 trial led to inclusion of anti-PD-1 therapy with standard of care gemcitabine/cisplatin chemotherapy in patients with unresectable biliary tract cancer (BTC), the improvement in overall survival is modest: 12.8 vs 11.5 mos. Identification of novel immunotherapeutic strategies remains a high priority. We discovered Galeazzi-9 (Gal-9), a carbohydrate-binding protein, is expressed in BTC; it has various immunosuppressive effects, including induction of apoptosis in T cells upon binding to its receptor Tim-3. Defining the role of Gal-9 in the BTC microenvironment will inform how to leverage it as a novel therapeutic target. Methods: Tissue microarrays (TMAs) were constructed from 66 patients who underwent curative-intent resection of BTC from 2000-2015 at our institution. These TMAs underwent immunohistochemical staining for Gal-9, CD4, CD8, and Tim-3. The percent of cells expressing each antigen was quantified. For each marker, martigale residual plots and bias-adjusted log rank tests were used to identify a cut-off value of "low" versus "high" expression where survival difference was maximal. For in vivo mouse experiments, the syngeneic BTC cell line URCACA4.3 was injected subcutaneously into the flank of C57BL/6 mice, followed by 3 weeks of treatment with anti-Galeazzi-9 or anti-Tim-3 antibody alone or in combination with anti-PD-1 antibody. Tumor-infiltrating lymphocytes (TILs) were analyzed by flow cytometry. Results: Median overall survival (mOS) was significantly improved in patients with high Gal-9 expression in their tumor. First Author: Ash those with low (32.5 mos vs 17.6 mos, p=0.018). However, when patients with high Gal-9 expression were further stratified according to Tim-3, patients with both high Gal-9 & high Tim-3 expression had significantly worse mOS than those with low Tim-3 (22.7 mos vs 113.9 mos, p=0.003), implying that interaction between Gal-9 and Tim-3 yields significant impact on TIL function. There was no difference in OS based on Tim-3 expression alone. When mice bearing BTC tumors were treated with Gal-9 or Tim-3 antibody monotherapy, there was no significant change in tumor growth versus control, but when either was used in combination with PD-1 inhibition, there was a significant reduction in tumor burden at study endpoint. Mice treated with either dual therapy had a significant decrease in CD4+ Treg and increase in CD4+ effector memory TIL populations compared to monotherapy (p<0.05). Conclusions: This study provides unique insight into the role of targeting the Gal-9/Tim-3 pathway in BTC. Our clinical data highlights that co-expression of these markers in BTC tumors is associated with significantly worse OS. Our in vivo pre-clinical studies demonstrate that blockade of either Gal-9 or Tim-3 synergizes with PD-1 targeted antibodies for superior anti-tumor efficacy. Research Sponsor: None.

556 Poster Session

Integrated multi-omics profiling to dissect the spatiotemporal evolution of metastatic hepatocellular carcinoma. First Author: Yun-Fan Sun, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Comprehensive molecular analyses of metastatic hepatocellular carcinoma (HCC) are lacking. Methods: Here, we generated genomic, transcriptomic, and cell repertoire data coupled with digital pathology and digital spatial profiling of 275 primary, 28 relapsed, and 176 metastatic regions from 182 HCC patients. Results: Primary tumors rich in hypoxia signatures tended to give rise to polyclonal dissemination, which was associated with a poor clinical outcome. Genomic divergence between primary and metastatic HCC was high, and early dissemination was prevalent. The remarkable neoantigen intratumor heterogeneity observed in metastases was associated with decreased T cell reactivity, which may have resulted from disruptions to neoantigen presentation. We identified macroevolutionary somatic copy number alterations as highly selected events driving metastasis. Furthermore, we found that subclonal Wnt pathway mutations were not selected during spreading, whereas subclones without Wnt mutations showed a strong selective advantage for metastasis and were characterized by a reactive microenvironment rich in activated fibroblasts favoring an invasive tumor cell phenotype. Finally, metastases without Wnt mutations exhibited higher enrichment of immunosuppressive B cells that mediated terminal exhaustion of CD8+ T cells via HLA-E – NKG2A checkpoint axis. Conclusions: Collectively, our results provide a multi-dimensional dissection of the complex evolutionary process of metastasis. Research Sponsor: None.
Agrin as a prognostic biomarker in hepatocellular carcinoma. First Author: Ankita Kapoor, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Hepatocellular carcinoma (HCC), the predominant form of hepatic cancer is associated with high mortality rates, both in the United States & globally. Alpha-fetoprotein (AFP) & Glypican-3 have been proposed as biomarkers for HCC, although they do not offer any prognostic insights into early disease progression. Immunotherapy combinations increase patient survival to ~18 months but are associated with high mortality rates, both in the United States & globally. Alpha-fetoprotein (AFP) & Glypican-3 are the most commonly used markers for HCC diagnosis, but they have limited predictive value.

Methods: Co-alterations in BTC with ARID1A, BAP1, and/or SMAD4 were linked to smoking history. The mean agrin levels were significantly higher in smokers (9.49 ng/ml) vs non-smokers (7.24 ng/ml). To further explore these findings, we investigated the association between agrin levels and smoking history.

Results: Of 217 patients screened, 160 patients were included in the final analysis. The mean age of the cohort was 63 years, and the majority were females (55%). In the order of frequency, intrahepatic cholangiocarcinoma (77.5%) and carcinoma of the Gallbladder (6.9%) were diagnosed. Molecular profiling was performed in 688 patients, and most (74%) were 80 years of age when the sample was obtained. Of patients with inactivating TSC1 and TSC2 alterations, 37.6% were in TSC1 and 62.4% were in TSC2 and included short variants (31.3% & 48.4%), rearrangements (2.7% & 6.6%), and copy number deletions (3.5% & 7.4%), respectively. TSC2 was less common (16.9% of patients, and most patients had microsatellite stable (MSS; 71.3%) tumors. Other commonly mutated genes in this cohort were TP53 (62.7%), APC (38.5%) and KRAS (30.4%). Conclusions: TSC1 and TSC2 alterations were commonly observed in GI cancers other than colorectal cancer. These and other findings suggest that these are actionable alterations that may be candidates for targeted therapy.

Atriptin: Atriptin is being tested in the PRECISION 1 (NCT05103358) trial which is open for enrollment or just-in-time clinical trial sites and available to patients with GI cancers harboring TSC1 or TSC2 alterations. Research Sponsor: Atriptin Bioscience.
Serologic, radiographic, and tissue-based markers associated with major pathologic response after treatment with neoadjuvant immunotherapy in patients with resectable hepatocellular carcinoma. First Author: Ashutosh Goel, MD, FACP; First Institution: Memorial Sloan Kettering Cancer Center, New York, NY; Second Institution: University of Pennsylvania, Philadelphia, PA.

Background: Neoadjuvant immunotherapy can induce a major pathologic response (MPR) in patients with resectable hepatocellular carcinoma (HCC), which may be associated with prolonged recurrence-free survival. This study aimed to understand which variables correlate with achieving an MPR.

Methods: Patients with resectable HCC who received either neoadjuvant nivolumab plus ipilimumab or nivolumab alone and underwent surgery were included. 18 patients had baseline and post-treatment computed tomography, alpha-fetoprotein (AFP), and elastography. 17 of these patients had baseline and post-treatment tissue available for immunohistochemistry. Patients were classified into two groups: MPR, defined as necrosis >70%, and no MPR. Data was summarized using descriptive statistics and compared using Wilcoxon rank sum test. P value <0.05 was considered statistically significant.

Results: Statistically significant differences in objective response (ORR) and changes in AFP, ALT, and PD-1 expression were identified upon comparison of patients with an MPR to those without an MPR (Table 1). Additionally, numerical differences in baseline tumor size, change in AFP, and tumor size in cirrhosis, and change in CDS, Graebe 2, and PD-1 expression after receipt of neoadjuvant immunotherapy were associated with achieving an MPR in patients with resectable HCC.

Research Sponsor: None.

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Survival and progression-free survival in patients undergoing curative resection for intrahepatic cholangiocarcinoma. First Author: Nazli Begum Ozturk, MD; First Institution: Massachusetts General Hospital, Royal Oak, MI.

Background: Intrahepatic cholangiocarcinoma (ICC) is a relatively rare but increasingly prevalent form of primary liver cancer. Surgical resection with negative margins is the mainstay of the treatment for patients with resectable ICCA. However, given the rarity of ICCA and its low resectability rate, well-defined prognostic markers and outcomes for patients undergoing curative hepatopancreatobiliary surgery are lacking. We aimed to analyze the characteristics and outcomes of patients undergoing liver resection for ICCA.

Methods: All consecutive patients with confirmed ICCA who underwent hepatectomy between 7/2006-3/2023 at our institution were included. Patients who received neoadjuvant therapy were excluded. Demographic, clinical, radiological, histopathological, recurrence, and survival data were collected. Overall survival was calculated from the date of liver resection to the date of death or last clinical encounter. Continuous variables are reported as median and interquartile range (IQR) 1 and IQR3, and categorical variables as counts and percentages.

Results: A total of 83 patients (43 male, 40 female) were included in the final analysis. The median age at resection was 67 years (56.0-74.0). Historically proven liver disease was present in 36.12% and liver cirrhosis was present in 9.53% of patients. Among all patients, hypertension was present in 61.44%, diabetes mellitus in 25.30%, inflammatory bowel disease in 7.22%. The median tumor size was 4.4 cm (3.0-6.2). Tumor histologic grade was 55.42% moderately differentiated tumor, 37.3% poorly differentiated tumor, and 7.22% well differentiated tumor. Of all patients, 37.66% had lymph node invasion, 35.61% had perineural invasion, and 30.76% had vascular invasion on liver histology. Positive surgical margins were present in 20.73% of patients. The duration from liver resection to the last follow-up or death was 1.6 years (8.0-3.20). The 1-, 3-, and 5-year survival-free survival rates were 72.78, 34.95, and 15.88 respectively. The 1-, 3-, and 5-year overall survival rates were 90.99, 65.94, and 42.42 respectively. Advanced ICCA at stage (p=0.001), presence of lymph node metastasis (p=0.03), vascular invasion (p=0.02), and age<50 (p=0.01) were associated with significantly worse overall survival. There was no statistically significant survival difference between patients with concurrent liver disease and those without (6.88 vs 12.79 years, p=0.46).

Conclusions: Our results demonstrate that ICCA has a substantial risk of recurrence despite curative surgery. The presence of advanced stage at diagnosis, lymph node involvement, vascular invasion, and age<50 were associated with significantly worse overall survival. Liver disease had no significant effect on the survival outcomes. Prognostic markers of recurrence and survival in patients vary in the literature and remain to be validated.

Research Sponsor: None.

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Surrogates for overall survival in advanced hepatocellular carcinoma: A meta-analysis. First Author: Yacoub Saleh, Princess Margaret Cancer Centre, Toronto, ON, Canada.

Background: Recent advances in systemic therapies have resulted in improved overall survival (OS) for patients with advanced hepatocellular carcinoma (HCC). The most common endpoint and primary endpoint for clinical trials in HCC is OS. Recent systematic reviews, that focused on surrogate endpoints (SEP) can reduce time and financial costs of future trials and accelerate regulatory approvals of new therapies. We conducted a literature-based meta-analysis to evaluate SEPs for OS in HCC. Methods: Randomized controlled trials evaluating systemic therapies in aHCC published 2007-2023 were identified through a systematic literature search of Cochrane and Medline databases as well as data abstracted presented at ASCO and ESMO meetings. Hazard ratios (HR) for OS and progression-free survival (PFS) and the time to progression (TTP) were extracted. ΔORR was calculated as the difference in overall response rates (ORR) between control and experimental arms. Pearson correlation and mixed-effects meta-regression analyses were performed. Surrogate threshold effect (STE) was determined for each comparison when possible. A p<0.05 was considered to be statistically significant.

Results: 26 trials were identified in the first setting with 14,827 patients and 11 trials in the subsequent-line setting with 5,316 patients. In first-line trials, immunotherapy (IO) is associated with higher ORR than other agents (p<0.003). There are statistically significant correlations between HRs of PFS/TTP/OS and ORR and OS. The relationship between HR-PSF and HR-OS persists in trials with or without IO, but only in trials enrolling< 30% patients of non-viral aetiologies. In subsequent-line trials, there are statistically significant correlations between HRs of PFS/TO/OS and TTP. (Table). For HR-PSF is 0.68 and 0.87 respectively for first- and subsequent-line trials. Conclusions: There are moderate to strong correlations between PFS and OS in aHCC in first-line and subsequent-line trials. STE for HR-PSF of 0.68 in first-line and 0.87 in subsequent-line settings can guide sample size calculation in future clinical trials. Research Sponsor: None.
Preoperative weight loss program for hepatocellular carcinoma patients with high body mass index in hepatectomy. First Author: Yu Saito, Department of Surgery, Yokohama University, Yokohama, Japan

**Background:** This study aimed to investigate the usefulness of a weight-loss program (WLP) in patients with a high body mass index (BMI) prior to liver resection (HR) for hepatocellular carcinoma (HCC). **Methods:** Among 445 patients with HCC who underwent initial Hx between 2000 and 2020, 19 with a high BMI (≥25.0) were enrolled in our WLP since 2014. For calorie restriction, the amount of energy consumed was calculated as the standard body weight (SBW) kg × 20–25 kcal/day. Protein mass was calculated as SBW kg × 1.0–1.2 g/day to maintain skeletal muscle mass. Patients also performed both aerobic and resistance exercises. The before-and-after changes were compared, and the effect of WLP on the short- and long-term results was investigated.

**Results:** The average length of WLP was 21 days, and weight loss was successfully achieved in all patients. Body fat mass was reduced during the program, while skeletal muscle mass was maintained. WLP led to improvements in liver function and fibrotic markers, without tumor progression. There were no postoperative complications (≥Clavien–Dindo [CD] III). A retrospective comparison of postoperative outcomes revealed that those in the WLP group showed a significantly shorter operation time and improved postoperative morbidity rate (≥CD III) with decreased postoperative hospital stay. There were no significant differences in long-term prognosis based on participation in the WLP.

**Conclusions:** WLP with multidisciplinary intervention improved short-term outcomes after Hx in patients with HCC and a high BMI. Research Sponsor: None.

**567 Poster Session**

**Association of congestive heart failure (CHF) with incidence rates of enteric infections and gram-negative sepsis (GNS) in patients with hepatopancreato-biliary cancers (HPBCs).** First Author: Himil Mahadevia, University of Missouri Kansas City, Kansas City, MO

**Background:** Chronic CHF leads to volume overload and can cause bowel wall edema. This may compromise local immune defense and promote increased translocation of gut bacteria into the blood. HPBCs can cause biliary tract obstruction which is also associated with bacteriaemia. Additionally, cancer treatments are associated with an increased risk of Clostridium difficile infection (CDI), regardless of antibiotic exposure. While associations between cancer and increased infection rates are well-established, we questioned whether concomitant CHF increases this risk further in the HPBC population. We therefore investigated whether concomitant CHF and HPBC influenced CDI, other infectious gastroenteritides (IGE), GNS rates or all-cause hospital mortality. **Methods:** A retrospective study was conducted by obtaining patients with HPBC through the application of specific ICD 10 codes from the National Inpatient Sample 2020. A large publicly available database of inpatient hospital stays incorporating data from hospitals across 48 U.S. states. Among this cohort, patients with chronic CHF were further identified by applying all CHF-specific ICD 10 codes. All patients with HPBC were divided into two groups, one with CHF (group A) and the other without CHF (group B). Outcomes were compared between the two groups using multivariate regression analysis (MVARA) adjusting for demographic factors, hospital-specific characteristics like location, bed size, etc., comorbidities including obesity, diabetes, hypertension, prior cardiovascular events, HIV, CKD, OSA, etc., prior coronary intervention/surgery as well as alcohol, smoking or substance use. Research Sponsor: None.

**Results:** 40.55% of patients were identified with HPBC. 39.5% were female. 18,955 patients (9.95%) were patients with HPBC. 20,072 patients with high body mass index in hepatectomy. 3.82 (1.71 - 8.56) .001. Sex (male vs female) 1.86 (1.04 - 3.32) .036. BMI (kg/m2) (≥25.0 vs <25.0) 0.70 (0.39 - 1.35) .463. Smoking (yes vs no) 1.61 (0.95 - 2.68) .071. Alcohol (yes vs no) 1.20 (0.61 - 2.39) .606. Cholesterol (≥200.0 vs <200.0) 0.98 (0.44 - 2.16) .912. HDL (≥40.0 vs <40.0) 2.72 (1.31 - 5.67) .037. Viral hepatitis (yes vs no) 1.95 (0.70 - 5.44) .294. Liver Cirrhosis (yes vs no) 1.20 (0.43 - 3.73) .738. Biliary inflammation 0.55 (0.29 - 1.09) .070. (Cholecystolithiasis + Cholecystitis vs no) 0.29 (0.13 - 0.69) .001. Surgical T stage (T1 + T2 vs T3 + T4 0.56 0.001. Surgical N stage (N1 + N2 vs N0) 0.47 (0.25 - 0.76) .001. Pathology differentiation (Non-well vs Well) 0.69 (0.25 - 1.96) .463. WBC 0.99 (0.93 - 1.06) .881. AST 1.00 (1.00 - 1.00) .584. ALT 1.00 (0.99 - 1.00) .773. Bilirubin 0.86 (0.75 - 1.00) .099. Total protein 0.85 (0.79 - 0.92) .001. Albumin 0.39 (0.23 - 0.69) <.001. Albumin-Globulin ratio (≥1.0 vs 0.1 - 1.0) 0.16 (0.06 - 0.40) <.001. BUN 0.90 (0.39 - 2.15) .001. Creatinine 0.18 (0.06 - 0.56) .001. gcc 0.86 (0.03 - 1.45) .001. PT INR 0.94 (0.76 - 1.16) .329. CA19-9 (≥39.0 vs <39.0) 1.72 (0.54 - 5.51) .001.

**Conclusions:** Advanced pathologic stage and high inflammatory marker levels, reflecting high tumor burden, were related with poor surgical outcome. Interestingly, high HBsAg level was related to reduced WLP as well. In conclusion, active screening for early detection, reducing inflammatory conditions, and managing diabetes might enhance ENS after R0 resection of GB cancer. Research Sponsor: None.

**568 Poster Session**

**A novel image-guided laparoscopic liver resection with integrated fluorescent imaging and artificial intelligence: A preliminary study.** First Author: Yoshikito Tashiro, Showa University, Shinagawa-Ku, Japan

**Background:** Technology innovations improve surgical techniques. ICG fluorescence imaging is beneficial for real time navigation tool during surgery and enables accurate tissue discrimination. The prediction of anatomical structures by artificial intelligence (AI) is expected to support surgeons as navigation tool. We developed a visual-support AI system to perform the laparoscopic liver resection (LLR) using ICG fluorescence imaging and AI technology. **Methods:** Procedure: ICG fluorescence imaging was used for liver mapping and securing surgical margin. AI model development and evaluation: Over 430 videos extracted from 13 videos of LLR for hepatocellular carcinoma and colorectal liver metastasis was used to develop and evaluate the AI algorithm at Anaut Inc. The annotation was performed on video frames capturing a LLR performed by 2 surgeons for 140s. ICG model development and evaluation: Over 430 images extracted from 13 videos of LLR for hepatocellular carcinoma and colorectal liver metastasis was used to develop and evaluate the AI algorithm at Anaut Inc. The annotation was performed on video frames capturing a LLR performed by 2 surgeons for 140s.

**Methods:** Imaging is beneficial for real time navigation tool during surgery and enables accurate tissue discrimination. ICG model development and evaluation: Over 140s videos extracted from 13 videos of LLR for hepatocellular carcinoma and colorectal liver metastasis was used to develop and evaluate the AI algorithm at Anaut Inc. The annotation was performed on video frames capturing a LLR performed by 2 surgeons for 140s. The AI model accurately recognized vascular structures of any size (IoU=0.33, $\mu=0.55$), and this AI system enabled to recognize and display these vascular structures through color-coding under bleeding and ICG fluorescent imaging without visual discrepancies. The AI model accurately recognized vascular structures of any size (IoU=0.33, $\mu=0.55$), and this AI system enabled to recognize and display these vascular structures through color-coding under bleeding and ICG fluorescent imaging without visual discrepancies. The AI model accurately recognized vascular structures of any size (IoU=0.33, $\mu=0.55$), and this AI system enabled to recognize and display these vascular structures through color-coding under bleeding and ICG fluorescent imaging without visual discrepancies. The AI model accurately recognized vascular structures of any size (IoU=0.33, $\mu=0.55$), and this AI system enabled to recognize and display these vascular structures through color-coding under bleeding and ICG fluorescent imaging without visual discrepancies. The AI model accurately recognized vascular structures of any size (IoU=0.33, $\mu=0.55$), and this AI system enabled to recognize and display these vascular structures through color-coding under bleeding and ICG fluorescent imaging without visual discrepancies. The AI model accurately recognized vascular structures of any size (IoU=0.33, $\mu=0.55$), and this AI system enabled to recognize and display these vascular structures through color-coding under bleeding and ICG fluorescent imaging without visual discrepancies.
HEPATOBLASTIC CANCER

Poster Session 569

The Effect of Obesity in Hospitalized Patients with Hepatocellular Carcinoma: A nationwide analysis. First Author: Exrem Turk, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Obesity, a prominent issue in global health, is known to increase the risk factors associated with a variety of cancers, including hepatocellular carcinoma (HCC), the most common type of primary liver cancer. While existing research affirms the heightened risk of developing HCC in individuals with obesity, there remains a significant gap in understanding the specific influences of obesity on the outcomes of patients admitted with primary HCC diagnosis during their index hospital admission. This study explores the mortality rate, length of stay (LOS), and healthcare utilization in HCC patients with and without obesity. Methods: Nationwide Inpatient Sample (NIS) was queried to determine adult hospitalized patients with a primary diagnosis of HCC using ICD-10 codes. The primary outcome was defined as the effect of obesity on inpatient mortality in those patients. Secondary outcomes included LOS, total hospital charge, health care utilization, and ICU admission. We evaluated the baseline characteristics using the t-test and chi-square test. Multivariable logistic regression analysis was performed to assess the association of HCC with obesity and inpatient mortality adjusted by age, gender, race, Charlson index, insurance, and household income. Results: A total of 62,050 HCC patients were identified, and 10.9% of these patients had obesity. HCC patients with obesity were younger (64.7 ± 6.5 years, p < 0.200), more likely to be female (32.2% vs. 24%, p < 0.001), White (59.8% vs. 50.2% p < 0.001), and more likely to have no insurance (28.8% vs. 23.3%, p < 0.001) compared to HCC patients without obesity. HCC with obesity had higher mean Charlson Comorbidity index 5.9 vs. 5.5, p < 0.001. The overall inpatient mortality rate was 2.2% for all patients who are admitted for HCC; lower in obese cohort vs. HCC with no obesity (1.9% vs. 3.3%, p = 0.001). In addition, HCC with obesity had a longer LOS mean 5.6 vs. 5.7 days (adjusted difference 0.6 ± 0.0 p < 0.001) and total hospital charges (mean $112,687 vs $88,481, adjusted difference $2122 ± 0.001). Also, ICU transfer rate and AKI development were found more in obese cohort and this different was statistically significant. Conclusions: Our study revealed that HCC patients with obesity had a lower inpatient mortality rate compared to those without obesity, despite longer hospital stays and higher costs. These findings hint at a complex interplay between obesity and HCC outcomes, necessitating further in-depth research. Research Sponsor: None.

Poster Session 570

Intrahepatic cholangiocarcinoma: Recurrence patterns, genomics and survival. First Author: Pratik Chandra, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Recurrence is common after resection of intrahepatic cholangiocarcinoma (IHC) but how recurrence patterns impact survival remains unclear. This study investigated the clinicopathologic and genomics factors associated with site of first recurrence and their impact on outcome after curative intent resection. Methods: Patients who underwent curative intent hepatectomy for IHC at two medical centers (MSKCC and EMC) with complete follow up and tumor genomic data were included. Documented sites of first disease recurrence were classified as liver only (LO), extrahepatic (EH) only or simultaneous liver and extrahepatic (SIM). Time to recurrence (TTR) and recurrence-free (RFS) were calculated from time of resection while OS was calculated from time of recurrence. Primary tumors underwent targeted next generation sequencing. Clinical, histopathologic and genomics factors associated with site of recurrence, RFS and OS were assessed. Results: A total of 318 patients (n=296 MSK, n=22 EMC) treated between 1993 and 2021 met inclusion criteria and were analyzed; 232 patients (73%) developed recurrence. TTR was 11 (9.8, 12.8) months; OS and RFS was 26 months (20, 33) and 14 (13, 18) months, respectively, among patients who recurred. Sites of first recurrence were LO 93 (40%), EH 80 (34%) and SIM 59 (26%). Median OS was similar in the LO (33 [26, 42] months) and EH groups (33 [24, 46] months) but much lower in SIM (12 [9, 18] months) (p < 0.001). Moderate/poor tumor differentiation (p = 0.004), LV (p = 0.004), N1 disease (p = 0.003), and PNI (p = 0.012) were associated with SIM; only positive resection margin predicted LO (p = 0.007). No individual genomic or pathway alterations predicted site of initial recurrence; however, for all patients, FGFR1 (HR 2.01, 1.4–2.84; p = 0.001), CDKN2A (HR 1.96, 1.29–2.91; p = 0.001) and CDKN2B (HR 3.2, 2.3–5.05; p < 0.001) and KRAS (HR 2.49, 1.56–3.96; p < 0.001) were associated with worse on multivariable analysis. SIM (HR 2.23, 1.49–3.34; p < 0.001), clinical stage III (HR 1.94, 1.26-2.99; p = 0.011), and alterations in TP53 (HR 2.07, 1.36–3.14; p < 0.001) and CDKN2A (HR 1.51, 1.2-2.53; p < 0.001) predicted higher risk of LO. Of note, 13 LO patients were treated with regional chemotheraphy after recurrence, with an associated median OS of 49 (33, NR) months compared to 28 (20, 39) months in the 80 patients treated with systemic therapy alone. Conclusions: Recurrence after resection of IHC was common, and the single most common site (66%). Clinicopathologic and genomics variables had limited ability to predict site of first recurrence. While LO and EH were associated with similar OS, simultaneous recurrences were dramatically worse. The data support adjuvant strategies targeting liver recurrence to improve outcome after resection of IHC. Research Sponsor: None.
TPS75

First-308: Phase III study of tenovertinib versus physician’s choice in patients with FGFR-altered, chemotherapy- and FGFR inhibitor-refractory/relapsed cholangiocarcinoma. First Author: Millid M. Javel, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA. Background: Fibroblast growth factor (FGFR) alterations occur in 10-15% of adult patients with advanced intrahepatic cholangiocarcinoma (CCA) and 1-2% of adult patients with advanced extrahepatic cholangiocarcinoma. The first generation FGFR inhibitors (FGFRi) pemigatinib and futibatinib, have been approved for the treatment of advanced CCA with FGFR2 alterations after systemic chemotherapy. However, disease progression occurs within 6-9 months. Secondary polyclonal mutations in the FGFR kinase domain represent a prominent acquired resistance mechanism. Tenovertinib, a novel multi-kinase inhibitor with high potency against a variety of FGFR2 kinase domain mutations, has shown promising clinical benefit in subjects with FGFR-altered metastatic CCA who were previously treated with chemotherapy and FGFR(i) in phase I/II clinical trials (NCT03654547, NCT04724599, NCT04919642). Methods: First-308 is a phase III, randomized, global multicenter study to evaluate the efficacy and safety of oral tenovertinib versus Physician’s Choice in subjects with FGFR-altered, chemotherapy- and FGFR(i)-refractory/relapsed CCA. Approximately 200 subjects will be enrolled in US, Europe, and Asia. Key eligibility criteria include age ≥ 18 years, ECOG performance status 0 or 1, documented FGFR2 fusion/rearrangement gene status, prior treatment with at least one line of chemotherapy and exactly one prior FDA-approved FGFR for unresectable or metastatic disease and Part B. The Part A is to select a dose for Part B. Eligible subjects will be randomized in a 2:2:1 ratio to receive tenovertinib 8 mg QD, tenovertinib 10 mg QD or Physician’s Choice (FOLFOX or FOLFIRI) in Part A or 2:1 in Part B to receive the recommended Part B dose or Physician’s Choice. The stratification factors at randomization include geographic region, prior lines of chemotherapy (1 or ≥ 2) and Physician’s choice. Tenovertinib will be administered orally QD in 28-day cycles. Subjects will continue to receive study treatment until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or termination of study by Sponsor, whichever occurs first. For Part A, the primary endpoint is safety/tolerability; secondary endpoints include objective response rate (ORR), duration of response (DOR) and PK analysis. For Part B, the primary endpoint is progression-free survival (PFS); secondary endpoints include overall survival (OS), ORR, DOR, safety, quality of life and population PK. Exploratory endpoints will assess the correlations between baseline FGFR2 alterations by cDNA and efficacy, and exposure-response in terms of efficacy and safety. Study is open for enrollment. Clinical trial information: NCT03249475. Research Sponsor: None.

TPS75

Trials in Progress Poster Session

Glutamine antagonist DRP-104 in combination with durvalumab in patients with advanced fibroblastic carcinoma (FLC) following progression on prior anti-PD(L)1 therapy. First Author: Mari N. DeZwaan, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA. Background: Fibroblastic carcinoma (FLC) is a rare, aggressive form of primary liver cancer predominantly affecting children and young adults under the age of 30. There is no established standard therapy and most patients with advanced disease succumb to their illness with a median prognosis of only 12 months. A chimeric transcript between $\text{DNJ}1$ and $\text{PRKAC}$, which encodes the catalytic subunit of protein kinase A ($\text{PKA}$), was recently identified as a signature genomic event in FLC. However, pharmacologic inhibition of PKA as a therapeutic approach in FLC has not been examined in preclinical or clinical trials. Of PKA for FLC with traditional small molecule inhibitors has been infeasible due to unacceptable on-target toxicity. Preclinical work from our laboratory and others has revealed that the $\text{DNJ1}-\text{PRKAC}$ fusion results in a metabolic rewiring of the tumor characterized by glutamine dependence. This glutamine dependence also creates a nutrient-depleted tumor immune microenvironment (TIME) enriched in immunosuppressive metabolites (e.g., ammonia, acidosis) that prohibits an effective antitumor immune response. Through this trial, we will test the hypothesis that glutamine antagonism in FLC resists resistance to immune checkpoint inhibitor (ICI) therapy through modulating the TIME. Methods: We are conducting a single-arm phase 1b/2 clinical trial of glutamine antagonist DRP-104 in combination with durvalumab in children (age ≥ 12) and adults with advanced FLC who have progressed on prior anti-PD(L)1 therapy. Patients will receive DRP-104 (145 mg s.c. twice weekly) in combination with a fixed dose of durvalumab (1500 mg i.v. every 28 days). The primary clinical endpoints are safety and objective response rate (ORR), defined as the percentage of patients achieving a complete response (CR) or partial response (PR) based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Secondary objectives include progression free survival (PFS), overall survival (OS), and immunological correlates. Key eligibility criteria include histologically confirmed FLC that is metastatic or unresectable; demonstrated radiographic progression on at least one line of prior anti-PD(L)1 therapy; Age ≥ 12; ECOG performance status 0 or 1; adequate organ function status per RECIST 1.1; and adequate end organ function. Patients will undergo normal core tumor biopsy pre-treatment and at approximately week 4. Biopsies will be used to prepare paraffin embedded and flash-frozen samples. Research bloodwork will be collected prior to dosing at baseline, prior to dosing on cycles 2-5, and every 3 months thereafter to be processed for PBMC isolation. This study has been registered under NCT06207086 and is expected to begin enrollment in December 2023. Clinical trial information: NCT06207086. Research Sponsor: None.

TPS75

Trials in Progress Poster Session

Sequential or up-front triple combination with durvalumab, tremelimumab, and bevacizumab for patients with unresectable hepatocellular carcinoma. First Author: Enrico N. De Toni, Klinikum der Universität München - Großhadern, CCC, München, Germany. Background: Escalation of treatment from one to two combined immune checkpoint inhibitors (ICI) has dramatically increased objective and clinical response in advanced hepatocellular carcinoma (HCC) patients. Establishing strategies with more than two CPI agents to further increase response while maintaining a manageable toxicity is therefore a top priority. The upfront simultaneous use of three or more CPI can yield a strong early response to treatment, but it may also increase treatment-related toxicity. An alternative approach, which prioritizes safety over immediate response, involves utilizing different CPI doublets in a sequential manner. However, this design entails switching to a different combination only after radiological progression is observed, and recurrent progressions may lead to deteriorating liver function and treatment discontinuation. Trials of immunotherapy of HCC conducted in recent years showed that the efficacious use of CPI, when used simultaneously, outweighs the drawbacks of their combined toxicity and that early radiological response to treatment, or the lack thereof, is a predictor of clinical outcome. In addition, failure of trials using broad-spectrum tyrosine kinase inhibitors (TKI) and CPI suggest that antibodies or narrow-spectrum TKI should be used for future CPI-based combinations in HCC studies. Based on these considerations, the MONTBLANC study is the first trial to assess the effectiveness of up-front triple treatment with a combination of the three currently approved immunological agents for HCC and to implement the concept of treatment escalation determined by lack of early radiological response (as opposed to treatment progression). Methods: The MONTBLANC study is a randomized, 2-arm phase II study on the efficacy of combinations of durvalumab, tremelimumab, and bevacizumab in patients with advanced HCC. Patients with preserved liver function (Child-Pugh A) with unresectable tumors or not amenable to local or locoregional treatment are randomized to an early escalation arm (A) or a triple combination arm (B). Patients in arm A receive durvalumab and tremelimumab (STRIDE regimen). Treatment will continue until confirmed disease progression, unacceptable toxicity, or based on RECIST 1.1, or in the absence of radiological response by the 4th month of treatment. Patients in arm B receive up-front STRIDE and bevacizumab. Treatment will continue until unacceptable toxicity or progression under the Bev-containing regimen. The primary endpoint is overall response rate (ORR). Clinical trial information: NCT01844466. Research Sponsor: None.

TPS75

Trials in Progress Poster Session

An open-label, multicenter study investigating RP3 oncolytic immunotherapy in combination with first- or second-line systemic atezolizumab plus bevacizumab in patients with locally advanced unresectable or metastatic hepatocellular carcinoma. First Author: Kevin Kim, University of Maryland School of Medicine, Baltimore, MD, USA. Background: Despite advances in treatment for unresectable hepatocellular carcinoma (HCC), long-term survival rates remain poor. The combination of atezolizumab (Atezo) plus bevacizumab (Bev) is approved frontline therapy for advanced HCC, but a minority of patients (pts) respond and secondary resistance usually occurs within months. HCC has an immune-suppressed tumor microenvironment (TME), mediated by activated immune checkpoints and angiogenesis pathways, which may contribute to therapeutic resistance. RP3 is a genetically modified herpes simplex virus type 1 (HSV-1) that expresses the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP^R), an anti–CTLA-4 antibody-like molecule, CD40 ligand, and 4-1BB ligand. The direct oncolytic effect coupled with immune stimulation by RP3 in the TME is intended to provide systemic antitumor activity and synergize with anti–PD-1/PD-L1 agents, such as Atezo. Preclinical data have demonstrated improved distribution of oncolytic HSV within tumors in combination with Bev, supporting the clinical combination of RP3 with Bev. This study will evaluate the safety and efficacy of RP3 combined with Atezo plus Bev as first-line (1L) or second-line (2L) systemic therapies for advanced HCC and bevacizumab in patients with advanced HCC. Key eligibility criteria include age ≥ 18 years, ECOG performance status 0 or 1, Eastern Cooperative Oncology Group performance status of 0 to 1. Key exclusion criteria include untreated hepatogenous or and/or gastric varices with bleeding or at high risk for bleeding and macroscopic invasion of the tumor into any major blood vessel(s) and/or portal vein(s). Pts with a history of medically refractory hepatic encephalopathy and/or hepato-renal syndrome are also excluded. Pts in the 1L cohort will receive Atezo 1200 mg QW for up to 12 weeks (QW) with Bev 15 mg/kg every 3 weeks (Q3W) with RP3 intratumorally Q3W for a total of 8 doses. Pts in the 2L cohort will receive Atezo every 2 weeks for 4 doses with Bev Q3W beginning on cycle (C)1 day (D)1, then RP3 and Bev Q3W for up to 12 more doses with Atezo Q3W being added on Q1D. The primary endpoint is the overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints are safety, ORR using HCC modified RECIST, duration of response, complete response rate, and progression-free survival. Clinical trial information: NCT07535958. Research Sponsor: Replimune, Inc.
A phase 1b/2 study to evaluate the safety and efficacy of TTI-101 as monotherapy and in combination in advanced hepatocellular carcinoma. First Author: Farshid Dayani, Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, Orange, CA

Background: STAT3 (signal transducer and activator of transcription 3) is a key regulatory protein positioned at the intersection of many signaling pathways integral to the survival and immune evasion of cancer cells. Persistent STAT3 activation has been linked to pathological conditions, including chronic inflammation and fibrosis, both of which play essential roles in the pathogenesis of hepatocellular carcinoma (HCC), and is observed in up to 95% of HCC cases. TTI-101 is a first-in-class, orally delivered, small molecule, direct inhibitor of STAT3 activation. TTI-101 monotherapy demonstrated tumor growth arrest as well as reversal of liver injury and fibrosis in a genetically modified mouse model (HepPten) which recapitulates the pathogenesis of HCC in non-alcoholic fatty liver disease (NAFLD), as well as in combination with immune checkpoint inhibition in a humanized HCC mouse model. TTI-101 monotherapy was found to be well tolerated in a Phase 1 trial conducted in patients (pts) with advanced solid tumors (NCT03195699). Of 15 evaluable HCC pts, 60% demonstrated clinical benefit, including 20% confirmed partial responses (median duration=10.5 months). All pts were relapsed/ refractory to standard of care (SOC; median prior systemic therapy=2), including anti-PD-(L)-1 based therapy. Methods: NCT05440708 is a multicenter, open-label study, with the primary endpoints including safety and efficacy of TTI-101 as monotherapy and in combination with SOC agents. Patients are enrolled to one of three treatment cohorts based upon prior therapy. Cohort A: TTI-101 (monotherapy), pts who have received up to 3 prior lines of systemic therapy. Cohort B: TTI-101 + pembrolizumab, pts who have progressed following ≥2 cycles of first-line anti-PD-(L)-1 based therapy. Cohort C: TTI-101 + atezolizumab/bevacizumab, patients who are systemic treatment-naive. The study consists of 2 parts for each cohort (Phase 1b and Phase 2). During Phase 1b, up to 3 dose levels of TTI-101 will be tested for each cohort to determine the RP2D, using a 3+3 design. Subsequent to RP2D determination, enrollment to Phase 2 will commence (Cohort A n=30, Cohort B n=30, Cohort C n=40). Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation based on investigator discretion, or study termination. Secondary and exploratory endpoints include pharmacodynamic effects of TTI-101 and evaluation of candidate biomarkers for anti-tumor activity. TTPS78

FusionVAC22_01: A phase I clinical trial evaluating a DNAJB1-PRKACA fusion transcript-based peptide vaccine combined with immune checkpoint inhibition for fibrolamellar hepatocellular carcinoma and other tumor entities carrying the oncogenic driver fusion. First Author: Michael Bitzer, Department for Internal Medicine I, Center for Personalized Medicine, Cluster of Excellence IFT (EXC2180), Eberhard-Karls University, Tübingen, Germany

Background: The DNAJB1-PRKACA fusion transcript is the driver of tumor pathogenesis in fibrolamellar hepatocellular carcinoma (FL-HCC) as well as in other tumor entities, e.g. oncogenic neoplasms of the pancreas and bile duct, thus representing a broad target for novel therapies in cancer. Recently, the DNAJB1-PRKACA fusion protein was identified as a source for HLA-presented neopeptides that can be targeted by T-cell-based immunotherapy (Bauer et al. Nat. Commun., 2022). The DNAJB1-PRKACA fusion-derived neopeptide FusionVAC-22 is in silico predicted to bind to 1,290 HLA class I alleles and contains HLA class I ligands from at least 13 of the 20 most frequent HLA class I alleles that cover 93.8% of the world population with at least one HLA allotype, enabling the broad application of FusionVAC22-based immune therapies. The first application of FusionVAC-22 based peptide vaccines adjuvanted with the TLR1/2 agonist XS15 emulsified in Montanide ISA 51 VG in two FL-HCC patients was well tolerated and showed the induction of profound and long-lasting T-cell responses. Of note, T-cell responses were accompanied by progression-free survival of both patients for so far 32 months and 13 months, respectively. Methods: Based on these encouraging results, we established a Phase I open-label, multicentric clinical trial to evaluate the immunogenicity along with safety and toxicity, as well as first signs of efficacy of the FusionVAC-22 based peptide vaccine in combination with the immune checkpoint inhibitor (ICI) atezolizumab, in 20 patients with locally advanced or metastatic FL-HCC or other malignant diseases that carry the DNAJB1-PRKACA fusion transcript. Further, key eligibility criteria include the absence of autoimmune phenomena due to prior immunotherapy agents (≥ grade 3) as well as tissue or organ allografts. The FusionVAC-22 based peptide vaccine is applied twice in a 4-weekly interval with the opportunity of a booster vaccination after 11 months. Atezolizumab application starts on day 15 after first vaccination and is continued 4-weekly for 1 year, followed by a 6-month follow-up. The primary objectives of the trial are immunogenicity, in terms of immune competent peptide-specific T-cell responses within 28 days, as well as safety and toxicity of the peptide vaccine in combination with ICI. Safety assessment is based on the frequency of adverse events according to CTCAE v5.0. Clinical efficacy will be determined by iRECIST assessment on imaging. Furthermore, disease control rate, quality of life as well as overall and progression free survival will be assessed. Clinical trial information: NCT0597295. Research Sponsor: Eberhard-Karls University Tübingen, Germany E.03.28048.2; Roche Pharma AG.

Lenvatinib in recurrent hepatocellular carcinoma after liver transplantation. First Author: Mehmet Akce, Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL

Background: Liver transplantation is a curative treatment option in hepatocellular carcinoma (HCC) however; up to 20% of patients develop recurrent disease. HCC recurrence post-transplant is usually extrahepatic (up to 67%) hence requires effective systemic therapy options. Available data are limited and restricted to small non-randomized studies and case series. Lack of prospective clinical trial data and limited data indicates an area of unmet need in treatment of recurrent HCC after liver transplantation. This phase II study aims evaluate the safety and efficacy of lenvatinib in patients with recurrent HCC after liver transplantation. Methods: This is a multi-institutional phase II trial with lenvatinib in patients with recurrent HCC after transplantation. Lenvatinib is administered 12 mg daily orally in patients ≥60 kg, and 8 mg daily orally in patients <60 kg. Every cycle is 28 days. Restaging scans will be performed every 8 weeks. Eligible patients must have histologically proven HCC that has recurred after liver transplantation and not amenable for surgical resection, age ≥18 years, ECOG PS 0-1, Child Pugh Class A, measurable disease per RECIST version 1.1, adequate organ function, no prior systemic therapy with lenvatinib or another systemic therapy in the post-transplant setting. Prior liver directed therapy is allowed, should be at least ≥28 days prior to the study enrollment, and should have at least one measurable untreated lesion by RECIST 1.1 Primary endpoint is overall response rate (ORR). Secondary endpoints are safety/tolerability, progression free survival, and overall survival. Pre-treatment and on-treatment peripheral blood samples will be collected for correlative research. A Simon’s two stage Minimax design is employed (hi; ORR = 5%; lo; ORR = 4%; Type I error = 0.05, power = 80%). In the first stage, 11 patients will be accrued, and if there is no objective response among them, the study will be stopped for futility. Otherwise, additional 6 patients will be accrued for a total of 17 patients. This study is currently enrolling patients. Clinical trial information: NCT05103904. Research Sponsor: None.

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Phase I/II clinical trial of regorafenib plus durvalumab (MEDI4736) in patients with chemotheraphy-refractory advanced biliary tract cancers. First Author: Raed Moft’d Taisseer Al-Rajabi, University of Kansas Cancer Center, Westwood, KS

Background: Biliary tract cancers (BTC) are a heterogeneous group of cancers affecting the epithelial lining of the intra- and extrahepatic portions of the biliary tree, ranking as the second most prevalent primary liver cancer after hepatocellular carcinoma. A subgroup of BTC was found to have an abundant tumor specific neoantigen expression, enriched expression of immune related genes and genes regulating inhibitory immune checkpoints. Recent advances in BTC treatment includes the addition of immunotherapy agents, which established the survival advantage of adding durvalumab to the gemzar + cisplatin regimen with an estimated 24-month overall survival rate of 24.9% versus 10.4% for placebo. The hazard ratio for progression-free survival favored durvalumab at 0.75 (95% CI, 0.59 to 0.98; P<0.001). Objective response rates also showed improvement, with 26.7% for durvalumab and 18.7% for placebo. Furthermore, single agent regorafenib has exhibited efficacy in patients with refractory advanced metastatic cholangiocarcinoma, particularly in terms of progression-free survival, favoring regorafenib over placebo, the overall toxicity profile was as expected. Regorafenib targets multiple tyrosine kinases and has been reported to show immunomodulatory properties that may counteract tumor-induced immunosuppression, providing a rationale for combining it with checkpoint inhibitors. We believe that modulating the tumor microenvironment with small molecule inhibitors like regorafenib will have synergistic effect when combined with checkpoint-based immunotherapy like durvalumab in patients with chemo-refractory BTC.

Methods: This study comprises a single-arm, unblinded Phase I/II trial designed to assess the safety and efficacy of the combination therapy involving regorafenib and durvalumab in patients with chemo-refractory advanced BTC. The Phase I portion employed a 3 + 3 design with two dose levels of regorafenib (80 mg and 120 mg) administered in conjunction with 1500 mg IV durvalumab every 28 days. Phase I safety was collected, and the Data Monitoring Committee (DMC) endorsed the continuation of the trial as planned. Eligibility: Historically confirmed unresectable or metastatic disease. Progressed on at least one line of therapy. May have received checkpoint inhibitor in the past. Inclusion criteria also include ECOG PS 0-1. Objectives: Primary Phase I: Safety of regorafenib in combination with durvalumab. Phase II: Progression-free survival (PFS), Secondary: Disease Control Rate (DCR), Overall response rate (ORR), Overall survival (OS). Statistical Plan: Interim futility testing after one year, halting if conditional power < 20%. Final analysis: PFS and OS via Weibull Regression. Enrollment is currently ongoing with 8 out of 40 patients enrolled. Research Sponsor: Bayer and AstraZeneca.

TPSS82 Trials in Progress Poster Session

A phase II study to evaluate the safety and efficacy of anlotinib combined with penpulimab for advanced refractory biliary tract cancer. First Author: Li Meng, General Surgery Department, The Second Affiliate Hospital of Air Force Medical University/Tangdu Hospital, Xi’an, China

Background: Although with modest efficacy, mFOLFOX is recommended as standard second-line chemotherapy for advanced biliary tract cancer (BTC). Several clinical trials are exploring the combination treatment of antiangiogenic drugs and immune checkpoint inhibitors. Anlotinib is an oral multi-targeted tyrosine kinase inhibitor targeting VEGFR1/2/3, FGFR1-4 and PDGF{sub}αβ, which effectively blocks tumor neo-vascularization and growth. Previous Phase II/III clinical trials suggested that anlotinib combined with PD-(L)1 inhibitors as second-line therapy was well tolerated and showed clinical anti-tumor activity in advanced biliary tract cancer (NCT03825705, NCT03996408, ChiCTR1900022003, ChiCTR2000037847). Penpulimab is a novel humanized anti-POD-1 IgG1 antibody with complete removal of Fc receptor mediated effect, and featuring slow antigen binding off-rate and high receptor occupancy. In this study, we explore anlotinib plus penpulimab as a chemo-free combination for second-line and above therapy. Methods: This is a prospective, single-arm, phase II study. BTC patients (pts) failed after the first-line treatment, aged 18-75 and an ECOSG PS of 0-1 were recruited. Eligible pts received anlotinib (12mg, po, d1-14, q3w) and penpulimab (200mg, iv, d1, q3w) until disease progression, unacceptable toxicity or up to 2 years. The primary endpoint was Objective Response Rate (ORR). Secondary endpoints included Overall survival (OS), Progression-Free Survival (PFS), Disease Control Rate (DCR) and safety. Based on a two-sided test for one proportion with 5.0% type I error, 80% power to detect an improvement in ORR from 5% to 22%, there will be 27 pts enrolled considering 20% of pts dropping out. Clinical trial information: ChiCTR200006126. Research Sponsor: None.

TPSS84 Trials in Progress Poster Session

Atezolizumab and bevacizumab in combination with TACE for patients with BCLC B HCC. First Author: Stacey Stein, Yale Cancer Center, New Haven, CT

Background: The combination of atezolizumab and bevacizumab (AB) is an effective regimen for patients with advanced HCC. Moving effective systemic therapy to earlier stages of HCC is a priority in improving outcomes. Assessing the safety of the combination of AB and TACE is essential to evaluating this emerging treatment option. This is an open-label, single arm pilot study. The primary objective of this study is to examine the safety and tolerability of AB with TACE. The secondary objectives are response rate, time to progression, overall survival, time to TACE progression (TTTP), and time to unachievable progression. Approximately 24 patients will be enrolled. AB will be given every 3 weeks (A: 1200 mg; 15 mg/kg) weeks and TACE will be planned for each patient to be completed in up to 4 treatments. B will be held for cycles that are within 4 weeks before or after each TACE. Imaging will be every 8 weeks for the first year, then every 12 weeks for the second year. Based on data from the GO30140 and the IMBrave 190 studies, we assume the rate of grade 3 or higher AEs is approximately 55% for AB and will likely be higher with the addition of TACE. Safety will be continuously monitored using the Bayesian Predictive Probability (PP) approach. The PP that the rate of grade 3 or higher AEs is related to the combination is greater than 70% by the end of the trial based on toxicity data in the current stage will be continuously updated. Inclusion criteria includes patients over 18 years old with an ECOSG PS of 0 or 1, no cirrhosis or Child-Pugh A cirrhosis, diagnosis of HCC by imaging or biopsy, and EGD within 6 months with no evidence of gastroesophageal varices with bleeding or high risk of bleeding unless treated. Patients are excluded if they are candidates for curative intent therapy, have had hepatic encephalopathy in the last 12 months, have occlusion of the hepatic artery or portal vein, or have history of significant autoimmune disease. 1. Finn, Richard S., et al. New England Journal of Medicine 382.20 (2020): 1894-1905. 2. Lee J and Liu D. Hepatobiliary Cancer 2021. By September 2023, 15 centers in Germany have been activated and 23 out of 40 planned centers. Study start of the ADJUBIL trial was in June 2021. The ADJUBIL trial comprises a single-arm, unblinded Phase II clinical trial of regorafenib plus durvalumab (MEDI4736) in patients with chemotheraphy-refractory advanced biliary tract cancers. First Author: Xiaojun He, General Surgery Department, The Second Affiliate Hospital of Air Force Medical University/Tangdu Hospital, Xi’an, China. This study comprises a single-arm, unblinded Phase I/II trial designed to assess the safety and efficacy of the combination therapy involving regorafenib and durvalumab in patients with chemo-refractory advanced BTC. The Phase I portion employed a 3 + 3 design with two dose levels of regorafenib (80 mg and 120 mg) administered in conjunction with 1500 mg IV durvalumab every 28 days. Phase I safety was collected, and the Data Monitoring Committee (DMC) endorsed the continuation of the trial as planned. Eligibility: Historically confirmed unresectable or metastatic disease. Progressed on at least one line of therapy. May have received checkpoint inhibitor in the past. Inclusion criteria also include ECOG PS 0-1. Objectives: Primary Phase I: Safety of regorafenib in combination with durvalumab. Phase II: Progression-free survival (PFS), Secondary: Disease Control Rate (DCR), Overall response rate (ORR), Overall survival (OS). Statistical Plan: Interim futility testing after one year, halting if conditional power < 20%. Final analysis: PFS and OS via Weibull Regression. Enrollment is currently ongoing with 8 out of 40 patients enrolled. Research Sponsor: Bayer and AstraZeneca.
TPS585  Trials in Progress Poster Session

PRECISION 1: A phase 2, multicenter, open-label basket trial of nab-sirolimus for malignant solid tumors harboring pathogenic inactivating alterations in TSC1 and TSC2. First Author: Dustin A. Deming, University of Wisconsin Carbone Cancer Center, Madison, WI

Background: SEER data report that US patients with advanced gastrointestinal (GI) cancers have a poor prognosis as indicated by low 5-year survival rates in patients with colorectal (15.6%), liver (3.5%), and other GI cancers, highlighting the need for more efficacious treatments. Dysregulation of the mTOR pathway contributes to tumor growth and disease progression in many cancers, including GI cancers. The tumor suppressor genes TSC1 and TSC2 are critical negative regulators of mTOR activity whose inactivation can lead to tumor cell growth. Inactivating TSC1 or TSC2 alterations have been observed in GI cancers with a combined frequency of up to 6.5% in hepatocellular carcinoma, 1.7% in colorectal adenocarcinoma and gastrointestinal stromal tumors, and 1.6% in cholangiocarcinoma. nab-Sirolimus, approved in the US for patients with advanced malignant perivascular epithelial cell tumor (PEComa), is an albumin-bound mTOR inhibitor (mTORi) that inhibits the mTOR pathway via suppression of the mTORC1 complex. In an exploratory analysis of the pivotal AMPECT trial of nab-sirolimus in advanced malignant PEComa (NCT02945476), 8/9 (89%) and 1/5 (20%) patients with inactivating alterations in TSC2 and TSC1, respectively, had a confirmed response. Most treatment-related adverse events were grade 1/2 (none were grade ≥4) and were consistent with mTORi-class adverse events. Based on the clinical observations from AMPECT and the underlying mechanism of action of nab-sirolimus, the PRECISION 1 trial was designed to assess the safety and efficacy of nab-sirolimus in a tumor-agnostic study of patients with advanced cancers harboring TSC1 or TSC2 inactivating alterations. The trial is open to patients with GI cancers with inactivating alterations in TSC1 or TSC2. Methods: In PRECISION 1 (NCT05103358), eligible patients are ≥12 years old and mTORi-naive, have advanced malignant solid tumors harboring TSC1 or TSC2 inactivating alterations identified using next-generation sequencing (NGS) of tumor tissue or liquid biopsy (confirmed by central review of NGS reports), and have received appropriate standard treatments, per investigator. nab-Sirolimus 100 mg/m2 is given intravenously over 30 min on days 1 and 8 of each 21-day cycle. The primary endpoint is overall response rate per independent radiographic review (IRR) using Response Evaluation Criteria in Solid Tumors v1.1. Other endpoints include duration of response, time to response, progression-free survival by IRR, overall survival, patient-reported quality of life, and safety. Enrollment began in March 2022. Collaboration with leading NGS vendors is expanding the identification of patients with qualifying TSC1 and TSC2 alterations; ongoing study access is facilitated through a just-in-time approach to trial location activation. Clinical trial information: NCT05103358. Research Sponsor: Aadi Bioscience.

TPS586  Trials in Progress Poster Session

Phase II study evaluating the efficacy of PDS0301 in combination with hepatic artery infusion pump (HAIP) and systemic therapy for patients with metastatic colorectal cancer or intrahepatic cholangiocarcinoma. First Author: Jonathan Matthew Hernandez, National Cancer Institute, Bethesda, MD

Background: Treatment of advanced liver tumors continues to pose significant challenges. Despite advances in immunotherapies, including immune checkpoint blockade, responses in colorectal liver metastases and biliary tract cancers remain suboptimal. The lack of robust clinical efficiency is likely myriad, including immunosuppression by the tumor microenvironment and poor susceptibility of these tumors to immune infiltration and surveillance. Interleukin-12 (IL-12) is a pro-inflammatory cytokine with extensive anti-tumor properties, but therapeutic development of recombinant human IL-12 (rHL-12) was halted due to significant systemic toxicities. PDS0301 (formerly M9241) is a novel human monoclonal antibody (NHS76) fused to two IL-12 heterodimers. The NHS76 antibody specifically targets histone/DNA complexes in regions of cellular necrosis resulting in accumulation within tumors. Importantly, recent Phase I trials have shown PDS0301 monotherapy to be well tolerated. We hypothesize that synchronization of PDS0301 administration with tumor cell death induced by locoregional and systemic chemotherapies will demonstrate increased efficacy over standard of care therapy. Methods: This is a single-center, non-randomized Phase II study to determine the safety and efficacy of PDS0301 in combination with fluoruridine (FUDR) administered by hepatic artery infusion pump (HAIP) and systemic chemotherapies in patients with either unresectable metastatic colorectal cancer (mCRC) or intrahepatic cholangiocarcinoma (ICC). Eligibility criteria include histologically or cytologically confirmed colorectal adenocarcinoma metastatic to the liver (Cohort 1) or unresectable intrahepatic cholangiocarcinoma (Cohort 2). Patients will receive HAIP-administered (FUDR) plus PDS0301 at a starting dose of 12mg/kg in 28-day cycles. Beginning in cycle 2, systemic chemotherapy with FOLFOX (Leucovorin, 5-Fluorouracil, and Oxalaplatin) or FOLFIRO (Leucovorin, 5-FU and Irinotecan) for mCRC or Gemcitabine and Oxalaplatin) for ICC will be introduced. Patients will be evaluated for response at eight-week intervals. The primary endpoint is overall response rates to PDS0301 and HAIP/systemic combination therapy. Secondary objectives include hepatic progression-free survival (PFS), extra-hepatic PFS, overall survival, and safety. Scientific objectives include determination of microenvironment alterations through pre- and post-treatment biopsies as well as evaluation of peripheral immune subsets and cytokines. To date, we have enrolled 8 of 23 patients in Cohort 1. Clinical trial information: NCT05286814. Research Sponsor: None.

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Repeat peptide receptor radionuclide therapy in neuroendocrine neoplasms: A NET Center of Excellence experience. First Author: Udaynir Singh Grewal, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Lu-177 DOTATATE Peptide Receptor Radionuclide Therapy (PRRT) was FDA approved in the United States in 2018 however this treatment modality has been widely available in European nations since early 2000s. Therefore, the data for the safety and efficacy of repeat PRRT are almost exclusively from European centers. We present a real-world experience with repeat PRRT in a cohort of US patients.

Methods: We used our single-center longitudinal IRB approved neuroendocrine tumor (NET) registry to identify patients who had been previously treated with at least 1 dose of PRRT (PRRT 1, either Lu 177 DOTATATE or Y90 DOTATOC) and following disease progression were retreated with a second course of PRRT (PRRT 2). Patients who received alpha PRRT were not included. We reviewed patient, tumor and treatment characteristics, time to progression after PRRT 1 and PRRT 2 and toxicity. Results: A total of 153 patients received at least 1 dose of Lu-177 DOTATATE PRRT at our institution post FDA approval, out of which, 13/153 (8.5%) patients received repeat PRRT. 2/13 patients were excluded due to lack of adequate follow up. All patients included were white (11/100%). Median age of the participants was 65 years (IQR 63, 67) and 54.5% (6/11) patients were females. Most patients had grade 2 (9/11, 81.8%) followed by grade 1 (2/11, 18.2%) and all except one patient included had a gastroenteropancreatic origin NET (10/11, 90.9%). 45.5% (5/11) patients received Lu-177 DOTATATE PRRT only both for PRRT1 and PRRT2, while 54.5% (6/11) patients received Y90 DOTATOC PRRT for PRRT1. Median number of lines therapies before PRRT1 and PRRT2 were 2 (IQR 2, 5.5) and 1 (IQR 1, 2) respectively. Patients received a median of 3 (IQR 2, 4) and 3 (IQR 1, 4) cycles for PRRT1 and PRRT2 respectively. At first restaging scan after PRRT1 (3-6 months), 54.5% and 46.5% patients had partial response (PR) and stable disease (SD) respectively. At first restaging scan after PRRT2 (3-6 months), 45.5%, 27.3% and 9.1% patients had SD, progressive disease (PD) and PR respectively; 2/11 patients (18.2%) died before first restaging scan. Median PFS for PRRT1 (n=11) was 22.5 months (IQR 12.7, 30.7). Median PFS (n=5) for PRRT2 was 10.9 months (IQR 10.05, 25.7). PFS was not reached for 1 patient after PRRT2. 1 (9.1%) patient each developed grade 2 nephrotoxicity and grade 3 thrombocytopenia after PRRT2. Conclusions: To our knowledge, this is the first of its kind analysis describing the safety and effectiveness of repeat PRRT in a US cohort. We show that repeat PRRT may benefit select patients and has an acceptable safety profile. Larger prospective clinical studies are required to identify patient groups that are more likely to benefit from repeat PRRT. Research Sponsor: None.

Quality of surveillance in patients with completely resected gastroenteropancreatic neuroendocrine tumors. First Author: Gordon Taylor Moffat, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: The incidence and prevalence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is increasing worldwide. Surgery remains the only curative modality. Because of limited data on patterns of recurrence, real-world surveillance practices and duration vary widely. In 2018, the Commonwealth Neuroendocrines Tumour Research Collaboration (CommNETs) published consensus surveillance guidelines for patients with completely resected GEP-NETs. Our aim was to assess adherence to the CommNETs guidelines for surveillance practices for this patient population at our center. Methods: We conducted a retrospective cohort study of patients with GEP-NETs seen for a new patient appointment at Princess Margaret Cancer Centre (PMCC) from 2019 to 2022. Patients were included if they had Surveillance guidelines were completed GEP-NET and followed on surveillance at our center. Demographic and tumor characteristics, surveillance practices, and clinical outcomes were abstracted. Summary statistics and a descriptive comparison of surveillance practices were completed. Results: Out of the 374 new patient appointments, 87 met the inclusion criteria. The main reasons for exclusion were metastatic disease at presentation (n=128), primary tumor not resected (n=58), and patients not followed at PMCC (n=49) so their surveillance practices cannot be determined from our records. The primary tumor sites were pancreatic (n=50, 57%), appendiceal (n=15, 17%), small bowel (n=11, 13%), rectal (n=10, 12%), and colon (n=1, 1%). Thirty-eight patients (44%) had stage 1 disease, 21 patients (24%) had stage 2, and 28 patients (32%) had stage 3. Forty-six patients (53%) had a WHO tumor grade of 1, 36 patients (41%) had grade 2, and 5 patients (6%) had grade 3. The median duration of follow-up was 18.2 months. Adherence to ordering the recommended surveillance investigations was 23% (20/87). Within the adherent cases, there was a higher number of appendiceal, WHO grade 1, and stage 1 tumors. Sixty-six patients (76%) had at least one test that was not recommended by the guidelines. The most frequent unnecessary tests were CT chest in all patient groups and CT pelvis in pancreatic NETs (Table). Six patients were lost to follow up and none discharged from surveillance. Conclusions: Adherence to the CommNETs' consensus guidelines was low at our center. The guidelines had a major impact on surveillance practices and providing an area for improvement in process of care and resource utilization. Research Sponsor: None.

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NEUROENDOCRINE/CARCINOID

592 Poster Session

Assessment of hematological toxicity in patients with advanced neuroendocrine tumors and extensive/innumerable bone metastases undergoing lutetium-177 DOTATATE treatment. First Author: Osama M Mosalae, Mayo Clinic Florida, Jacksonville, FL.

Background: The introduction of peptide receptor radionuclide therapy (PRRT) using Lutetium-177 (177Lu) DOTATATE has led to a paradigm shift in the treatment of neuroendocrine tumors (NETs). Hematological toxicity is a well-recognized adverse effect (AE) of 177Lu DOTATATE. Most cytopenias are transient, with an estimated incidence of 10%-25%, typically mild to moderate in severity (grade 1-2). The most dreaded AE of PRRT is therapy-related myeloid neoplasm (t-MN), with an estimated 2%-8% incidence and a higher incidence reported in patients who also received prior chemotherapy. We sought to evaluate the hematological safety of 177Lu DOTATATE in the setting of NETs with extensive (i.e., innumerable) bone metastases. Methods: We retrospectively reviewed the medical records of all major Mayo Clinic pts (patients) with extensive/innumerable osseous metastases, defined as >50% skeletal involvement by positron emission tomography (PET) DOTATATE, who were treated with 177Lu DOTATATE. Pt characteristics and laboratory results were collected before, during, and after 177Lu DOTATATE treatment. Hematotoxicity was graded according to the NC-I-CTCAE v5. Results: Out of 27 pts, 13(48%) developed cytopenia(s) of any grade after treatment with one or more cycles of 177Lu DOTATATE. In total, there were 13(48%) pts with anemia, 13(48%) with thrombocytopenia, and 6(22%) with neutropenia. Six (22%) pts had severe hematological toxicity (G3-G4). Twelve months post-PRRT, 7(26%) pts continued to experience cytopenia(s) of any grade, of whom 4(15%) had G3-4 hematotoxicity. One pt developed t-MN, and two pts had myelophthisis on bone marrow biopsy from infiltrating NET. 16(59%) pts received cytotoxic chemotherapy before PRRT, and 7(25.9%) developed subsequent cytopenia(s). Overall, 15(55%) pts completed four cycles, while 3 pts didn’t complete four cycles of 177Lu DOTATATE due to hematotoxicity. Conclusions: Pts with advanced NETs and extensive/innumerable bone metastases treated with PRRT could be at higher risk for myelosuppression than historical controls. Our study highlights the importance of carefully monitoring and assessing hematological parameters in pts being considered for 177Lu DOTATATE with extensive/innumerable bone metastases. Research Sponsor: None.

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Prognostic factors for overall survival in patients with advanced digestive neuroendocrine carcinoma treated with first-line cisplatin-based chemotherapy: A post-hoc analysis of JCOG1213. First Author: Hidekazu Hirano, National Cancer Center Hospital, Tokyo, Japan.

Background: Advanced digestive neuroendocrine carcinoma (ADNEC) is a rare and aggressive malignancy without evidence of prognostic factors assessed in prospective studies. We aimed to evaluate prognostic factors in patients with ADNEC receiving first-line cisplatin-based chemotherapy. Methods: This is a post-hoc analysis of JCOG1213, which is a phase 3 randomized trial showing equivalent overall survival (OS) for cisplatin plus etoposide versus cisplatin plus irinotecan as first-line chemotherapy for patients with ADNEC. The primary endpoint of JCOG1213 was OS. For this post-hoc analysis, prognostic factors, patients who had ineligible histology based on the central pathological review or who lacked the necessary clinical data for analysis were excluded. A Cox proportional hazard model was used to assess the effect of independent variables on OS. Priori variables selected on previous reports (performance status (PS), Ki-67 index, and serum LDH level), as well as variables that remained at a level of p-value <0.20 by backward stepwise selection, were incorporated in the final model of OS. Results: Among 170 patients enrolled in JCOG1213, a total of 129 patients with ADNEC were included in this analysis. In multivariable analysis, serum LDH level (≥ upper normal limit vs. normal) was identified as a significant prognostic factor for OS (HR = 1.721, 95% CI: 1.144–2.589, p = 0.009). Other clinicopathological factors were not found to be significant, including PS (1 vs. 0; HR = 0.784, 95% CI: 0.507–1.214, p = 0.276), Ki-67 (≥ 55% vs. <55%; HR = 1.475, 95% CI: 0.588–3.698, p = 0.407), liver metastasis (present vs. absent; HR = 1.434, 95% CI: 0.986–2.124, p = 0.072), sex (female vs. male; HR = 1.387, 95% CI: 0.937–2.053, p = 0.032), and serum ALP level (≥ upper normal limit vs. normal; HR = 0.948, 95% CI: 0.630–1.106, p = 0.789). Out of 20 GEP-NEC patients, 16 (70%) patients were observed to present with the POLE adenocarcinoma component. Stage III, IV, and recurrence were observed in 2, 16, and 2 patients, respectively. Progression-free survival and overall survival were compared between midgut and non-midgut NETs. Among the patients who did not develop disease progression or mortality during the treatment course, PFS and OS were compared based on dosing variations. Dosing variations were defined as "reduced" (50% of 7.4 GBq/cycle), "delayed" (>12 weeks between cycles), or "fewer" (<4 cycles) doses. Kaplan-Meier survival analysis with log-rank test was used for statistical analysis. Results: Median clinical follow-up was 18.7 months, during which disease progression and death occurred in 54 (50%) and 20 (18%) patients, respectively. Among the 98 patients with Ki-67 index ≥ 20%, those with non-midgut tumors (n=55) showed significantly shorter PFS compared to those with midgut tumors (n=43) with the hazard ratio of 2.0 (P=0.014, median of 15.6 vs. 26.9 mo). No difference in OS was found between the two groups (P=0.83). Among the 93 patients who did not develop disease progression or mortality during the course of PRRT, dosing variations were used in 23 patients. The types of dosing variations were “reduced” in 4 (17%) patients, “delayed” in 16 (70%) patients, and “fewer” in 7 (30%) patients. The reasons for dosing variations were hematologic in 9 (39%) patients, hepatic in 2 (9%) patients, renal in 1 (4%) patient, other medical in 3 (13%) patients, functional in 3 (13%) patients, and logistical in 6 (26%) patients. No difference in PFS (P=0.40) or OS (P=0.24) was found based on presence or absence of dosing variations. Conclusions: Patients with non-midgut NETs show approximately twice the rate of disease progression over time following PRRT than those with midgut NETs. Administering reduced, delayed, or fewer doses of PRRT may still offer comparable benefit compared to the recommended dosing. Research Sponsor: None.

595 Poster Session

Advances in the treatment of gastroenteropancreatic poorly differentiated neuroendocrine carcinoma at our hospital. First Author: Shinichi Nishina, Department of Medical Oncology, Kurashiki Central Hospital, Okayama, Japan.

Background: Overall survival after first-line chemotherapy for metastatic or recurrent gastroenteropancreatic poorly differentiated neuroendocrine carcinoma (GEP-NEC) is poor. The types of dosing variations in combination with etoposide or irinotecan in GEP-NET patients have been used as first-line chemotherapy for GEP-NEC patients, but no standard treatment has been established for second-line and subsequent chemotherapy. Recently, however, we have seen patients with a good prognosis after treatment based on comprehensive cancer genomic profiling (CPG). We retrospectively reviewed all patients with a good prognosis after the CPG test who were treated with chemotherapy. In this study, we describe treatment strategies and the outcomes of patients who underwent cisplatin combination chemotherapy after PRRT treatment in GEP-NEC patients. Results: Median age was 71 (48 to 81) years, 16 were male, and primary sites were esophagus in 2 patients, stomach in 7 patients, small intestine in 2 patients, large intestine in 6 patients, and pancreas in 3 patients. Five patients had an adenocarcinoma component. Stage III, IV, and recurrence were observed in 2, 16, and 2 patients, respectively. Progression-free survival and overall survival were compared between midgut and non-midgut NETs. Among the patients who did not develop disease progression or mortality during the treatment course, PFS and OS were compared based on dosing variations. Dosing variations were defined as "reduced" (50% of 7.4 GBq/cycle), "delayed" (>12 weeks between cycles), or "fewer" (<4 cycles) doses. Kaplan-Meier survival analysis with log-rank test was used for statistical analysis. Results: Median clinical follow-up was 18.7 months, during which disease progression and death occurred in 54 (50%) and 20 (18%) patients, respectively. Among the 98 patients with Ki-67 index ≥ 20%, those with non-midgut tumors (n=55) showed significantly shorter PFS compared to those with midgut tumors (n=43) with the hazard ratio of 2.0 (P=0.014, median of 15.6 vs. 26.9 mo). No difference in OS was found between the two groups (P=0.83). Among the 93 patients who did not develop disease progression or mortality during the course of PRRT, dosing variations were used in 23 patients. The types of dosing variations were “reduced” in 4 (17%) patients, “delayed” in 16 (70%) patients, and “fewer” in 7 (30%) patients. The reasons for dosing variations were hematologic in 9 (39%) patients, hepatic in 2 (9%) patients, renal in 1 (4%) patient, other medical in 3 (13%) patients, functional in 3 (13%) patients, and logistical in 6 (26%) patients. No difference in PFS (P=0.40) or OS (P=0.24) was found based on presence or absence of dosing variations. Conclusions: Patients with non-midgut NETs show approximately twice the rate of disease progression over time following PRRT than those with midgut NETs. Administering reduced, delayed, or fewer doses of PRRT may still offer comparable benefit compared to the recommended dosing. Research Sponsor: None.

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598 Poster Session

Prognostic value of O-methylguanine-DNA methyltransferase (MGMT) status in pancreatic neuroendocrine tumors with capcitabine and temozolomide (CAPTEM). First Author: Eduardo Terán Brage, Hospital Universitario de Salamanca, Salamanca, Spain

Background: Loss of MGMT expression has been suggested as a predictor of response to alkylating agents in pancreatic neuroendocrine tumors (pNET), however, its determination is controversial. We aim to analyze the prognostic value of MGMT status assessed by immunohistochemistry (IHC) or pyrosequencing (PSQ) in patients with pNET receiving CAPTEM.

Methods: Retrospective and uncenteric analysis in patients (p) with pNET treated with CAPTEM from April 2008 to February 2023. MGMT deficiency was determined by IHC and MGMT promoter methylation by PSQ. We analyzed patients’ characteristics, progression-free survival (PFS) and overall survival (OS) according to MGMT status.

Results: 20p were included. Age (median): 62 (46-77). Males (45%). Tumor grade (G): G1 (15%), G2 (35%) and G3 (20%). MGMT deficiency was detected in 12p (60%) and promoter methylation in 10p (50%). Results by IHC were consistent with PSQ in 10p (50%) with mismatches in 4p (methylated MGMT and positive IHC) and 6p (unmethylated MGMT and negative IHC).

We reported a higher response rate in MGMT-deficient and MGMT-methylated (p) Table. In MGMT-deficient p we observed significantly better PFS (88m vs 11.1m; p=0.02, HR=0.21) and OS (141m vs 35.8m; p=0.03, HR=0.20). Also, in MGMT-methylated p we detected better PFS (88m vs 17.7m; p=0.20, HR=0.44) and OS (188m vs 141m; p=0.11, HR=0.28). A subanalysis was performed based on G, showing better PFS (88m vs 62m; p=0.03, HR=0.11) and OS (186m vs 35.8m; p=0.01, HR=0.06) in those with G2 vs G3.

There was a trend of improved OS by PSQ; the higher the probability of promoter methylation (r=16) -0.62; p<0.01. Conclusions: Our results support MGMT status, deficiency by IHC or promoter methylation by PSQ, as a potential prognostic biomarker in pNET treated with alkylating agents. However, it is necessary to evaluate its prognostic value in prospective studies.

Research Sponsor: None.

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Potential biomarkers for treatment response in advanced non-pancreatic neuroendocrine tumors. First Author: Sahithi Sonti, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Well-differentiated NETs are highly vascular and hence, inhibition of angiogenesis is of interest. VEGF, a key molecule in promoting angiogenesis, has also been reported to promote an immune suppressive microenvironment. Here we tested the hypothesis that an oral inhibitor of FGFR1-3, VEGFR1-3 and PDKFRGDA, has previously been evaluated in a phase II clinical trial in well-differentiated, non-pancreatic NETs, where 83% of the evaluable patients were progression-free at 16 weeks and median PFS was 11 months. In preclinical studies, nintedanib was shown to increase PD-L1 expression in tumor cells, which then results in improved outcomes with immune checkpoint inhibition.

In preclinical studies, nintedanib has been shown to increase PD-L1 expression in tumor cells, which then results in improved outcomes with immune checkpoint inhibition. The current study evaluated the potential of nintedanib in patients with advanced NETs who had failed to respond to regimens with, or without, a prior immune checkpoint inhibition agent.

Results: Of 246 patients, 164 (66.7%) had type 1, 2 (0.8%) had type 2, 52 (21.1%) had type 3, 18 (7.3%) were PPI-associated and 7 (2.8%) remained unclassified. Multifocal disease was more common for types 1 (56.1%) and 2 (40.0%) than type 3 (13.5%) and PPI-associated tumors (27.8%, P<0.001). Patients with type 3 GNET were also less likely to have WHO grade 1 tumors (26.9%) compared to other GNETs (type 1 37.2%, type 2 40.4%, P=0.040, P=0.500). Additional, distant metastases at presentation occurred more frequently with type 3 (38.5%) than type 1 (12.5%) and type 2 (20.0%), and PPI-associated tumors (11.1%, P<0.001). GNET type (type 1 vs 3, odds ratio [OR] 0.005 [95% confidence interval [CI] 0.001-0.050]; P=0.001) was associated with type 3, OR 0.13 [95% CI 0.010-1.33]).

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Conclusions: PPI-associated tumors may represent a distinct GNET type with intermediate outcomes compared to type 1 and type 3 tumors. However, factors other than type tumor must be considered determining survival. Research Sponsor: None.
Risk of second cancers in long term survivors of neuroendocrine tumors of the large intestine. First Author: Callie Fort, BSW Health, Round Rock, TX

Background: There is an increasing incidence of neuroendocrine tumors (NET) of the colon and rectum likely related to increased screening colonoscopy and availability of better diagnostics. Most of these tumors identified during screening are low grade early-stage tumors with high cure rates. Data on long term risk of recurrence of NET and other second cancers is lacking. We studied the incidence rates of all second malignancies in survivors of NET of the colon and rectum. Methods: We analyzed data from the Surveillance, Epidemiology and End Results (SEER), Research Data 17 Registries, Nov 2022 Sub (2000-2022) to determine the risk of second malignancies in patients with an initial cancer diagnosis of NET of the colon and rectum. With these criteria we had overall 17,907 patients and 157,720 patient years of follow up. The relative risk of subsequent malignancies is reported as a standardized incidence ratio (observed incidence/incidence expected if the population in question were perfectly matched to the general population). Incidence ratios are analyzed over time from initial diagnosis to assess long term risk. Results: Survivors of NET of the large intestine are at highest risk of malignancy of the rectum (O/E: 6.4; CI: 7.26 - 5.21; N=239) and this increased risk of rectal cancer persists even 10 years after the initial diagnosis (O/E: 3.8; CI: 5.37 - 2.6; N=32). There is no increased risk of cancer of the colon excluding rectum (O/E: 0.98; CI: 1.18-0.81; N=114). Even after 10 years from diagnosis there is increased risk of recurrence of the NET of the Colon (O/E: 1.28; CI: 1.55-1.06; N=110) and NET of the Rectum (O/E: 1.12; CI: 1.23-1.02; N=433). There is also increased incidence of small intestine cancer (O/E: 2.92; CI: 4.17-1.97; N=30). Prostate cancer (O/E: 1.28; CI: 1.41-1.15; N=400). Kidney and renal pelvis cancer (O/E: 1.53; CI: 1.86-1.25; N=104). Thyroid cancer (O/E: 1.68; CI: 2.12-1.32; N=55) and Nodal Non-Hodgkin Lymphoma (O/E: 1.34; CI: 1.71-1.03; N=64). Conclusions: Survivors of NET of the large intestine are at risk of developing subsequent malignancies. The information presented may help physicians in effectively monitoring survivors for second cancers at various timeframes from their initial diagnosis. Research Sponsor: None.

Phase 2 study of nab-sirolimus in patients with well-differentiated and advanced/metastatic neuroendocrine tumors of the gastrointestinal tract, lung, or pancreas. First Author: Michael J. Demeure, Hoag Memorial Hospital Presbyterian, Translational Genomics Research Institute, Newport Beach, CA

Background: Neuroendocrine tumors (NETs; ~2% of all malignancies) commonly arise from the gastrointestinal (GI) tract, pancreas, and lung, often presenting as metastatic disease. The PI3K/Akt/mTOR pathway is implicated in the pathogenesis and progression of NETs. Everolimus, an oral mTOR inhibitor (mTORi), is an option for treatment of NETs of the GI tract, lung, or pancreas but response rates observed in the RADIANT–3 and -4 studies were modest at 4–10%. nab-Sirolimus is a mTORi that utilizes nanoparticle technology to preferentially target tumors and is approved in the USA for malignant perivascular epithelioid cell tumor. In preclinical animal models, nab-sirolimus demonstrated higher intratumoral drug accumulation, improved target suppression, and stronger antitumor activity relative to equal weekly doses of sirolimus and everolimus, warranting further exploration of nab-sirolimus. This study will evaluate efficacy/safety of nab-sirolimus in patients with advanced/metastatic NETs. Methods: This phase 2, multicenter, open-label, single-arm study (NCT05997056) will enroll approximately 21 adults (>18 years) with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas who have received ≥2 prior lines of therapy, excluding somatostatin analogs (SSTs). Patients with functional NETs are eligible if they have been on a stable dose of SSTs for ≥12 weeks and had disease progression during SSTs treatment. Eligible patients must have ≥1 measurable target lesion (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), Eastern Cooperative Oncology Group performance status score 0 or 1, and adequate organ function/hematologic parameters. They are not permitted to have received prior mTORis, including nab-sirolimus, or to have tumors with known inactivating TSC1 or TSC2 alterations. Patients will receive nab-sirolimus 100 mg/m² by intravenous infusion on days 1 and 8 of 21-day cycles. Treatment will continue until disease progression or unacceptable toxicity, or until discontinuation based on investigator or patient discretion. The primary endpoint is investigator-assessed objective response rate per RECIST v1.1. Secondary endpoints include duration of response, disease control rate, time to response, progression-free survival, overall survival, and safety. Exploratory endpoints include correlation of baseline molecular biomarkers with clinical outcomes. Analysis of study objectives will be descriptive. Study site activation is underway with the first patient on study anticipated for the 3rd quarter of 2023. Clinical trial information: NCT05997056. Research Sponsor: Aadi Biosciences, Inc.
Addition of metastasis-directed therapy to standard-of-care systemic therapy for oligometastatic pancreatic ductal adenocarcinoma (PDAC): EXTEND. Results of a multicenter, randomized phase II trial. First Author: Ethel Lum. Department of Gastrointestinal Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Standard treatment of oligometastatic pancreatic ductal adenocarcinoma (PDAC) consists of multi-agent chemotherapy, although outcomes remain poor. We tested the hypothesis that the addition of comprehensive metastasis-directed therapy (MDT) to standard systemic therapy and unknowns in PDAC and other solid tumors with KRAS G12C mutation. Methods: Two phase 1/2 trials (NCT05009329 in China; NCT05002270 in US, Europe and Israel) are evaluating the safety and efficacy of glecirasib in patients (pts) with solid tumor harboring KRAS G12C mutations. As both trials have similar inclusion and exclusion criteria, we have pooled the data from them to assess the effect of glecirasib monotherapy in various types of solid tumor with low incidence of KRAS G12C mutation. Here we report the preliminary efficacy and safety results of glecirasib in pts with PDAC and other solid tumors (excluding NSCLC and CRC) from the pooled population of both trials. Results: As of Sep 8, 2023, a total of 48 pts have received glecirasib monotherapy (41 from NCT05009329 and 7 from NCT05002270) and 47 were evaluable for efficacy. This includes 28 PDAC and 19 other solid tumors (7 biliary tract, 3 gastric, 3 small bowel, 1 appendiceal, 1 hepatocellular, 1 peritoneal, 1 posterior bronchial mediastinal, 1 ameloblastic carcinoma and 1 cervical). At baseline, pts had previously received a median of 0 lines of systemic therapy (range: 0 to 4; with 23 pts having received one prior line); 85% Asian, 15% Caucasian; most (45 pts) at 800 mg qd. Among 28 pts with PDAC, 13 achieved confirmed partial response (PR) with the confirmed objective response rate (ORR) of 46.4% (13/28) and disease control rate (DCR) of 96.4%; the median duration of response (DOR) and progression-free survival (PFS) were 4.1 months and 5.5 months (95%CI 1.2, 13.1), respectively. Among other solid tumors, 19 pts were included in the study (13/28) with the median DOR and DCR of 84.2% (16/19) were observed; the median DOR and PFS were 8.3 months and 7.0 months (95% CI 1.1 to 15.2), respectively. Treatment-related AE (TRA) of any grade occurred in 89.6% (43/48) pts; the most common (>10%) TRAE were anemia (52.1%), blood bilirubin increased (39.6%), white blood cell count decreased (18.8%), AST increased (16.7%), ALT increased (14.6%), aspartate transaminase increased (10.4%), and nausea (10.4%); Grade 3 TRAE occurred in 25% (12/48) pts; no TRAE were fatal or led to treatment discontinuation. Conclusions: Glecirasib monotherapy is well tolerated and has a manageable safety profile and exhibits promising anti-tumor activity in pts with KRAS G12C mutated PDAC and other solid tumors. Further clinical development of glecirasib in above mentioned population is ongoing (NCT06008288). Clinical trial information: NCT05009329 and NCT05002270. Research Sponsor: Jacobo Pharmaceuticals Co., Ltd.
Socioeconomic variables in the National Cancer Database: Utilization and impact of income and education in survival models for patients with resected pancreatic cancer.

First Author: Qiyan Luo, University of Minnesota Medical School, Minneapolis, MN

Background: The National Cancer Database (NCDB) is commonly used for analyzing survival outcomes in pancreatic cancer and has a robust number of patient-specific socioeconomic variables. Although these aggregated variables are commonly collected, their utility and impact on survival has infrequently been assessed. We aim to quantify the distribution of income and education variables on their impact on survival models for patients who underwent resection for pancreatic ductal adenocarcinoma (PDAC). Methods: Patients undergoing definitive surgery for PDAC between 2004-2014 were identified from the NCDB. Variables of interest were income and education according to the patient's ZIP code of residence. Pearson and Spearman correlation was assessed. Overall survival (OS) was calculated using Kaplan-Meier method. The effects of income and education was calculated using Cox Hazard (PH) models. Results: 69,362 patients met inclusion criteria. Median OS was 16.6 (95% CI: 15.8-17.4) months. The correlation coefficient between income and education based on the 2020 American Community Survey data was 0.49 (p < 0.001). Median OS from the time of diagnosis was 21 months. The 5-year OS was 10.4 and 22.7 months for patients with lowest and highest education (p < 0.001). Patients with lower education had a 5-year OS of 22.4 months, comparable to the group with highest education (p = 0.82). The 5-year OS based on income quintiles was 18.7 and 22.5 months for the Q1 and Q5 (p = 0.01). Group with no income 

609 Poster Session

Socioeconomic variables in the National Cancer Database: Impact and trends in gastrointestinal cancers.

First Author: R. Adam Levine, Michigan Medicine, Ann Arbor, MI

Background: While multiple reports have suggested that the National Cancer Database (NCDB) presents strong for survival differences in gastrointestinal cancers based on income, research on education and survival remains underdeveloped in this patient population. This is likely due to the complexity of using the NCDB and the lack of NCDB education variables. Methods: We used the NCDB prostate cancer database to identify patients diagnosed with prostate cancer between 2004-2014 (N = 176,806). We explored differences in survival and trends in survival across income and education quintiles using the Kaplan-Meier method and multivariable Cox regression models. Results: We observed significant differences in survival for patients with different levels of income and education. Patients with lower income and education had worse survival outcomes than those with higher income and education. These differences were consistent across all gastrointestinal cancer types. Conclusions: Our findings highlight the importance of considering socioeconomic factors in the survival of patients with gastrointestinal cancers and suggest that interventions targeted at improving access to care and education may help improve outcomes for these patients.

610 Poster Session

Demographic and social vulnerability factors associated with late diagnosis of gastrointestinal cancers.

First Author: Muhammad Sohail Khan, UT Southwestern Medical Center, Dallas, TX

Background: Almost 30% of gastrointestinal cancers (GI) are diagnosed at an advanced stage. These patients have a poor prognosis with no curative options. Certain demographic and social factors adversely impact health outcomes. However, these have not been well studied in the context of late diagnosis of GI cancers. Methods: Texas and California cancer registries, merged with CDC’s Social Vulnerability Index (SVI) database, were used to identify patients diagnosed with gastrointestinal cancer from 2004 to 2019. To determine the association of demographic and social vulnerability factors, while accounting for differences in tumor characteristics, univariate and multivariate logistic regression analysis was performed for each cancer type. Results: In the PanCAN KYT patients were included. Of these 166,910 (78.3%) patients had metastasis at diagnosis. This included 55%, 39%, 21%, and 17% of all pancreatic, gastric, colorectal, and liver cancers, respectively. We observed that increased age, male sex, and higher income were associated with decreased odds of metastatic cancer at diagnosis. Conclusions: This study identifies multiple demographic and social factors associated with late diagnosis of GI cancers. Interventions towards these factors can help improve patient outcomes and reduce healthcare costs.

Factors associated with odds of metastatic cancer at diagnosis on multivariate logistic regression analysis performed for each cancer type:

<table>
<thead>
<tr>
<th>Factors*</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.98 (0.98–0.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.98 (0.98–0.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Income</td>
<td>0.98 (0.98–0.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Education</td>
<td>0.98 (0.98–0.98)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Factors associated with odds of metastatic cancer at diagnosis on multivariate logistic regression analysis performed for each cancer type.
Conclusions: early stage (stages I and II) and late-stage (stages III and IV) pancreatic cancer with an accuracy of 99.1% in pancreatic cancer individually. A comparative analysis was conducted employing chemotherapeutic agents, radiation, surgery, and recurrence-free survival (RFS) and overall survival based on race were analyzed. Results: The cohort (N=947) consisted of 147 (16%) African Americans (AA) and 775 (82%) Non-Hispanic Whites (NHW). The median age at diagnosis was 68 years (\pm 10) among AA and 70 years (\pm 11) in NHW. Thirty-seven (26%) of AA and 104 (14%) of NHW were current smokers; 46 (33%) of AA and 323 (45%) of NHW consumed alcohol regularly. Among AA, 32 (22%) were obese (BMI \geq 30), compared to 104 (25%) in NHW. Other comorbidities included diabetes (35% in AA vs. 32% in NHW) and acute/chronic pancreatitis (11% among AA vs. 9% among NHW). Eighteen percent (18%) of AA and 17% of NHW had stage II disease, 16% and 12% had stage III and 48% in both had stage IV disease respectively. The treatment modality consisted of chemotherapy (63% in AA vs. 66% in NHW), surgery (25% in AA vs. 26% in NHW) and radiation (10% in AA vs. 12% in NHW). The median time to treatment initiation was 30 (17, 41) months for AA and 26 (16, 40) months for NHW. On univariate analysis, AA race was associated with younger age at diagnosis (p = 0.043), higher current tobacco use (p = 0.001), lower alcohol use (p = 0.012), lower rates of obesity (p = 0.046) and higher rate of acute pancreatitis (p = 0.037) in pancreatic cancer. On multivariate analysis, race was not associated with difference in recurrence-free survival (12 months in AA vs. 14 months in NHW; p = 0.96) when adjusted for age, sex, alcohol use, tobacco use, cancer stage and chemotherapy. High mean age, clinical stage II, III and IV, current alcohol use, underweight and BMI \geq 30 and cerebrovascular accident as a comorbidity was associated with worse overall survival when adjusted for other variables. Conclusions: Our study revealed that pancreatic cancer in AA was diagnosed at a younger age, associated with active smoking and pancreatitis. We observe there was no difference in treatment initiation among AA and NHW. There was no significant difference in recurrence-free survival and overall survival compared to NHW when adjusted for other variables. Future studies incorporating germline mutations, novel biomarkers are needed to determine impact of racial health disparities on outcomes in pancreatic cancer. Research Sponsor: None.

A novel early cancer detection approach for pancreatic cancer. First Author: Maarten F. Bijlsma, Amsterdam UMC, University of Amsterdam, Laboratory for Experimental Oncology and Radiobiology, Center for Experimental and Molecular Medicine, Oncoide Institute, Cancer Center Amsterdam, Imaging and Biomarkers, Amsterdam, Netherlands Background: Pancreatic adenocarcinoma (PDAC) is commonly diagnosed at advanced stages, leading to high mortality rates. Earlier detection of PDAC is associated with improved long-term survival, but effective population-level screening is not available. There is therefore an urgent need to improve early detection of PDAC. Wholomics has developed a PDAC-specific proprietary early detection test, using cancer-specific molecular signatures for peripheral blood. A feasibility study was conducted in the analysis of serum samples from the Amsterdam UMC Liquid Biopsy Center. Three cohorts were included in this study: 1) A cohort of healthy control subjects, 2) patients with a histopathologically confirmed diagnosis of PDAC spanning stages I through IV, and 3) patients with a confirmed diagnosis of chronic pancreatitis. Peripheral blood samples of cancer patients were taken before treatment or surgery. Wholomics used its proprietary technology to quantitatively analyse all serum specimens. Disease-specific molecular signatures were identified and used to develop computational biomarkers specific to both pancreatic pathologies (chronic pancreatitis and pancreatic cancer) and to pancreatic cancer individually. A comparative analysis was conducted employing multiple machine learning algorithms, which were subjected to a 10-fold cross-validation procedure. The accuracy, specificity and sensitivity of the best-performing algorithm is reported. Results: This retrospective study included 50 healthy controls, 12 patients with chronic pancreatitis, and 42 patients with pancreatic cancer (12 stage I, 15 stage II, 9 stage III, 6 stage IV). Applying Wholomics' technology, an accuracy of 99.1% in differentiating between patients with chronic pancreatitis and pancreatic cancer patients was achieved. A specificity of 98.0% and a sensitivity of 100.0% were reached. Furthermore, pancreatic cancer patients and chronic pancreatitis patients were differentiated with 95.2% accuracy. Wholomics was also capable of differentiating between early stage (stages I and II) and late-stage (stages III and IV) pancreatic cancer with an accuracy of 99.0% in the overall cohort. Taken together, this study proves that disease-specific molecular signatures in peripheral blood can distinguish patients with PDAC from healthy individuals and patients with pancreatitis with very high accuracy. If validated in additional cohorts, this method could be evaluated as a screening test for PDAC to allow for early detection and improve patient outcomes. Research Sponsor: Wholomics GmbH.

Liquid biopsies for faster diagnosis of suspected advanced pancreatic and biliary tract cancers: ACCESS, a UK innovation programme. First Author: Lauren Jones, The Royal Marsden NHS Foundation Trust, London and Sutton, United Kingdom Background: Tissue diagnosis in biliary tract (BTC) or pancreatic (PC) cancer is often delayed due to anatomical location and patient (pt) factors (frailty, severe comorbidities). Approximately 25% of invasive biopsies are non-diagnostic, requiring repeat procedure. Most BTC and PC pts present with advanced disease. In stage III and IV solid tumours, Guardant360 (G360) 76 gene panel liquid biopsy (LB) detects ctDNA in 80%/85% of BTC/PC. ACCESS is a real-world innovation programme evaluating the impact of adding G360 to the current invasive diagnostic pathway for suspected BTC/PC in 6 hospitals in London (n=240). Methods: This is a pre-planned interim analysis of the first sequential 65 pts with G360 in ACCESS. Patients were aged >18 years, ECOG = 2 with high radiographic suspicion of stage III/IV BTC or PC without histological diagnosis at registration or other malignancies within 3 years. Positive LRs were reviewed at molecular tumour board with 4 pre-specified levels of diagnostic certainty: diagnostic/consistent/possibly/not consistent. Tumour board review followed. Endpoints include repeat biopsy rate, change in time to diagnosis, quality of life, health economic assessment and patient satisfaction. Results: 64 patients were analysed (1 excluded). 50% female, median age 73 years (43-94), suspected cancer sites 14%/77%/9% BTC/PC/either BTC or PC. Suspected stage III/IV disease 38%/62%. ctDNA detection rate was 80%/100%/82% in overall cohort/BTC/PC. Most commonly detected LB alterations in suspected BTC and PC patients were TP53, APC, ATM, CDK/TP53, KRAS, CDKN2A, ARID1A. In BTC and PC, diagnostic method was liquid biopsy alone/liquid and tissue biopsy/tissue alone in 16%/49%/33%. 17% had repeat biopsy. Sensitivity/ specificity of cancer diagnosis (all-comers) using liquid biopsy and tissue biopsy was 86%/95% (95% CI 13.9-68.4). Conclusions: There is a high ctDNA detection rate with high level diagnostic certainty, promising for future genomic transformation of BTC/PC diagnostic pathways, potentially reducing repeat invasive biopsies, speeding up diagnosis, facilitating precision therapy, with ACCESS defining a blueprint for molecular interrogation of liquid biopsies. Full recruitment is planned to complete in March 2024. Research Sponsor: NHS England.
615 Poster Session
The radiological morphology of mesopancreas: A new variable to predict a positive vascular margin after pancreatoduodenectomy for pancreatic ductal adenocarcinoma? First Author: Julie Navez, Hôpital Erasme, Hôpital Universitaire de Bruxelles, Bruxelles, Belgium

Background: The most frequently invaded surgical margins on pancreatoduodenectomy (PD) specimens of pancreatic ductal adenocarcinoma (PDAC) are vascular margins, especially the superior mesenteric artery ( SMA), also called mesopancreatic margin. Considering embryology, it may be hypothesized that PDAC cells tend to infiltrate the retroperitoneum through the contents of mesopancreas, justifying the frequent SMA positive margin. Because the radiological aspect of mesopancreas has been poorly studied, the aim of this original research was to assess the mesopancreatic infiltration on diagnostic imaging, corroborate with the corresponding margin pathology and evaluate the impact on survival in PDAC patients who underwent PD.

Methods: From 2015 to 2020, all patients who underwent PD for PDAC with curative intent were reviewed, excluding patients who lost to follow-up, who died postoperatively or within the first year for non-oncological reason, and those with unavailable preoperative imaging. Surgical margins of pathological specimens were reassessed. Blinded reviewing of preoperative radiographic images was conducted. According to qualitative assessment, the mesopancreas tissue was defined as normal fat (NF), fat stranding (FS) or solid infiltration (SI).

Results: 133 patients were included in the study, including 51 (38%) who received neoadjuvant therapy. The tumor location was into the head or the uncinate process in 54% and 46%, respectively. At diagnosis, PDAC were classified as resectable (51%), borderline resectable (28%) and locally advanced (9%) according to the NCCN classification. FS or SI in the mesopancreas were present in 45 (24%) and 18 (14%) patients, respectively. Tumor size on imaging, tumor location, chronic obstructive pancreatitis, vascular contacts and NCCN resectability status were predictive factors of mesopancreas infiltration (p<0.001). Median overall and disease-free survivals were significantly lower in case of SI compared to NF or FS. When comparing patients with mesopancreatic infiltration, the one whose received neoadjuvant therapy (n=20) to those who underwent upfront surgery (n=25), no significant impact was observed in survivals. R0 resection was obtained in 36%; in all patients with R1 resection, a vascular margin was involved. Tumor size at pathology, SMA margin and resection status were factors that were significantly influenced by the radiological infiltration of the mesopancreas. The SI of mesopancreas on diagnostic imaging was associated with a poor prognosis, but not FS, in patients who underwent PD for PDAC. SMA margin and resection status were correlated with the radiological texture of the mesopancreas, which suggests to further explore underlying mechanisms related to tumor invasion of vascular margin and mesopancreas.

Research Sponsor: Fonds Erasme.

616 Poster Session
Developing cell-free DNA (cfDNA) epigenetic signature (ep-Sig) for early detection of malignant transformation of intraductal papillary mucinous neoplasms (IPMN). First Author: Ashish Manne, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers with poor outcomes. Around 20% arise from premalignant lesions (PML) including IPMN. Current guidelines recommend risk stratifying IPMN based on the location, size, and imaging characteristics after first diagnosis, followed by endoscopic ultrasound (EUS) in high-risk populations, and annual or bi-annual imaging. This approach can be improved with cfDNA testing. Traditional mutation testing in cDNA evaluation is not useful secondary to their poor prevalence/detection rates. We propose ep-Sig to improve surveillance and early detection of PDAC transformation. Methods: We curated an 11-gene cfDNA ep-Sig from the literature with a proven role in the malignant transformation of IPMN. Evidence suggests that epigenetic changes in every gene of this panel have a role in carcinogenesis in IPMNs. We compared RNA gene expression of the genes in this ep-Sig between normal (NT) and PDA tissues using a web-based tool, TMMplot.com that uses the data from the Gene Expression Omnibus of the National Center for Biotechnology Information (NCBI-GEO) or Cancer Genome Atlas (TCGA). Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and The Genotype-Tissue Expression (GTEX) repositories was used create this tool. It uses Mann-Whitney or Kruskal-Wallis tests to compute statistical significance. We used cell-free epigenome atlas (CFAE) database to examine the prevalence of these markers in cfDNA of PDA patients. Results: RNA expression of all the genes from the ep-Sig combined was significantly lower in PDA than NT (0.45, p=1.3e-26). Gene expression was 8/11 genes was lower in PDA tissues than NT (0.44, p=3.1e-26). The other 2 genes were not detected in the tested samples. Prevalence of all the markers in ep-Sig was > 90%. Conclusions: Our proposed ep-Sig has a high prevalence in PDA patients and has reliable preliminary evidence in tissues suggesting its diagnostic value. This study is the first step in developing non-invasive cfDNA testing with the potential to improve the current surveillance strategies for IPMN pending larger prospective studies. Research Sponsor: None.

617 Poster Session
Amplified Sciences PanCyst Pro Panel to accurately identify non-mucinous pancreatic cyst fluid. First Author: Mini Thomas, Amplified Sciences, West Lafayette, IN

Background: Pancreatic cysts are rarely symptomatic, and, consequently, are detected incidentally during routine imaging analyses for unrelated disorders. Guidelines for diagnosing and managing pancreatic cysts are based on imaging characteristics alone during endoscopic ultrasound with fine-needle aspiration (EUS-FNA). Unfortunately, currently available protein markers and assays are not sufficiently accurate to rule-out patients in whom a non-mucinous pancreatic cyst has formed. Since non-mucinous pancreatic cysts seldom progress to cancer, this patient population is at risk of being subjected to unwarranted surveillance, testing, and possible surgical intervention. Furthermore, identification of mucinous pancreatic cysts does not establish the risk of progression to cancer (rule-in) or the need for surgical intervention. Methods: To address the unmet needs in pancreatic cyst diagnosis, Amplified Sciences has combined a panel of markers with a clinically translated surface enhanced Raman spectroscopy (SERS)-based protease activity assay as a rule-out diagnostic tool. The tri-analyte panel was tested on a cohort of 185 retrospective samples gathered from three separate institutions (UPMC, IU Health, and UCSF) and consumed only 12 µL of cyst fluid per sample. The goals of this study were to establish the negative predictive value (NPV) of this panel prior to transition to a CILA-regulated laboratory and create a preliminary algorithm for analysis. Results: The results of this statistically powered study showed that protease activity outperforms carcinoembryonic antigen (CEA), a current standard diagnostic marker for pancreatic cyst fluid, in sensitivity, specificity, and NPV. Furthermore, in combination, the tri-analyte panel identifies non-mucinous pancreatic cysts with 99% sensitivity and a negative predictive value ~95%. Conclusions: These results support the use of this panel in clinical settings as a diagnostic tool to rule-out patients from surgical intervention, as well as the use of SERS as an optical detection mode for clinical diagnostics. Future work will continue to address the unmet need for improved diagnostic information through multiplexed analyses of markers that consume comparatively minimal volume of pancreatic cyst fluid samples. Studies will also seek to build on the SERS platform by introducing more dyes, substrates, assays, and analytical methods. Amplified Sciences would like to acknowledge significant efforts to build the clinical samples cohort from Gina Zhu, Kelli Ifuku, and Dr. Kimberly Kirkwood from USCF, Christine Decapite and Dr. Randall Brand from UPMC, and Michele Yip-Schneider and Dr. C. Max Schmidt from IU Health. Research Sponsor: Amplified Sciences.

618 Poster Session
Pancratic biopsy evaluation with nsCanary: A "smart ROSE" device for feedback on sample adequacy and cancer presence in endoscopic biopsies—Initial human clinical trial results. First Author: Les Bogdianowicz, NovaScan, Chicago, IL

Background: Pancreatic cancer (PC) accounts for 0.5 million new cases and 4.7% of the world’s cancer-related deaths in 2020. Endoscopic ultrasonic (EUS) guided fine needle biopsies (FNB) are the current standard of care for confirming suspicious lesions, however the diagnostic accuracy is reported between 70-90%. Rapid on-site evaluation (ROSE) improves the diagnostic performances of biopsies to reduce the number of needle passes, complication rates, and the need for additional procedures. However, availability of an on-site pathologist is often not feasible. NovaScan has pioneered the use of an improvisation of a surgical pathology microscope to improve diagnoses. This study is the first step in developing non-invasive cfDNA testing with the potential to improve the current surveillance strategies for IPMN pending larger prospective studies. Research Sponsor: None.

Results: Sensitivity: 97.1%; Specificity: 86.7%; PPV: 86.2%; NPV: 94.6%.

Confusion matrix for nsCanary assessments and pathology outcomes.

Pathology Outcome

<table>
<thead>
<tr>
<th>nsCanary Assessment</th>
<th>CA</th>
<th>NC</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>95</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NC</td>
<td>5</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>PC</td>
<td>2</td>
<td>2</td>
<td>93</td>
</tr>
</tbody>
</table>

CA indicates cancerous outcome, NC indicates necroascentous outcome.
Clinical impact of KRAS mutations in metastatic pancreatic ductal adenocarcinoma (PDAC). First Author: Carter Horton, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: Mutations in the KRAS oncogene occur in most PDAC and lead to the activation of the KRAS protein. Little is known about the differential impact of KRAS mutations on the outcomes of patients receiving standard of care cytotoxic treatments for metastatic disease. KRAS inhibitors are emerging as promising options for this disease and understanding the impact of distinct KRAS mutations in patient outcomes is needed.

Methods: This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database of 5,369 patients. Adult patients with diagnosis of metastatic PDAC who received at least one line of systemic therapy and had sufficient data available were included in this analysis. Median time to next treatment (TTNT) and overall survival (OS) were calculated and compared for 3 lines of treatment in KRAS mutations. TTNT and OS were calculated for each permutation of treatment and each KRAS mutation. Hazard ratios (HR) were generated for each KRAS mutation and treatment, accounting for potentially confounding variables. Results: Of the 5,369 patients, 2,472 met the inclusion/exclusion criteria. G12C had the shortest median OS (7.5 mo) and G12D had the longest (9.1 mo). Overall, KRAS mutation-positive patients had a median OS of 8.6 mo, compared to 11.7 mo for KRAS Wild Type (WT) patients. A Cox Proportional Hazard analysis of OS across KRAS mutation status found that G12C, G12V, G12D, and Other Non G12/13 KRAS had significantly higher HR than KRAS WT. A comparison of the three common first-line interventions for metastatic PDAC showed that FOLFIRINOX had the longest median TTNT (5.3 mo) and the longest OS (10.2 mo), while Gemcitabine had the shortest TTNT (2.6 mo) and OS (5.9 mo). A Cox Proportional Hazard analysis of OS across all patients found that Gemcitabine and Gemcitabine with Nalidixic acid had significantly higher HR than FOLFIRINOX. FOLFIRINOX had the longest TTNT in the G12C, G12V, G12D, and Other non-G12/13 and KRAS WT groups (see table).

Conclusions: Our data suggest that FOLFIRINOX has a longer TTNT than other front-line regimens for KRAS G12C, G12V, G12D, and G12R. KRAS G12C was associated with the shortest OS among common KRAS mutations. Research Sponsor: None.

TTNT (mo) of first line treatments for each mutation group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall, N = 96</th>
<th>Upfront Surgery, N = 45</th>
<th>NACT+Surgery, N = 36</th>
<th>Chemotherapy, N = 15</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12C (n=33)</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>47.1 45.2 44.1 44.1 4.97 4.97 5.49 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>0.01</td>
</tr>
<tr>
<td>G12D (n=29)</td>
<td>52.8 51.4 54.9 57.4 2.0 2.0 2.0 2.0</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>0.01</td>
</tr>
<tr>
<td>G12V (n=34)</td>
<td>52.8 51.4 54.9 57.4 2.0 2.0 2.0 2.0</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>0.01</td>
</tr>
<tr>
<td>G13 (n=13)</td>
<td>Other Non G12/13 KRAS (n=130)</td>
<td>52.8 51.4 54.9 57.4 2.0 2.0 2.0 2.0</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>0.01</td>
</tr>
<tr>
<td>G12R (n=2056)</td>
<td>WT (n=516)</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>62.5 54.4 44.4 37.8 3.8 3.52 4.57 5.49</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Optimising utility of selective internal radiation therapy in metastatic pancreatic ductal adenocarcinoma. First Author: Prasad Cooray, Yarra Oncology, Melbourne, Australia

Background: Selective internal radiation therapy (SIRT) using Yttrium-90 containing microspheres has established benefit for a number of cancers but there is limited data available on the utility of SIRT for the treatment of metastatic pancreatic ductal adenocarcinoma (PDAC). Methods: In this retrospective audit we identified 32 patients who received SIRT using Yttrium-90 microspheres for metastatic PDAC in 2 treatment centres. All patients received SIRT in combination with chemotherapy. Data was analysed from electronic medical records. Results: Thirty two patients with metastatic PDAC who had SIRT were identified. Patients received SIRT (median activity 1.6 GBq) in combination with chemotherapy (platinum-based; n = 23, non-platinum-based; n = 9). Three patients remain alive and 29 patients were included in the survival analysis. For the entire group, the median OS was 15 months (range 4-49), median survival from time of SIRT was 9 months (range 1-48) and median PFS from time of SIRT was 4 months (range 1-25). Median PFS (6 vs 2 months, p=0.001) and OS (13 vs 4 months, p=0.0004) from SIRT was significantly better when SIRT was given with 1st-line therapy vs with 2nd-line and beyond. Median PFS from SIRT was significantly better (10 vs 2 months, p=0.0020) when combined with 1st line platinum-based chemotherapy (n=14) vs non-platinum based treatment (n=6). 18 month survival was 40% (n=13) with 9/13 patients having had SIRT with 1st line with platinum-based therapy. 24 month survival was 22% (n=7) with 7/7 patients having had SIRT with 1st line with platinum-based therapy. SIRT was well-tolerated with no associated 30-day all-cause mortality. Grade 3 adverse events were liver abscess (7%, n = 2), gastritis (7%, n = 2) and duodenitis (7%, n = 2). Conclusions: This is the first report to analyse optimum utility of SIRT with chemotherapeutic regimens in PDAC. Our data suggest SIRT in combination with 1st-line platinum agents contribute to the best outcomes in the setting and warrants further study. Research Sponsor: None.
623 Poster Session
Nutritional impact and prognostic role of systemic inflammatory response index (SIRI) in advanced pancreatic cancer: PANTHEIA-Spanish Society of Medical Oncology (SEOM) study results. First Author: Vilmar Pacheco-Barcia, Department of Medical Oncology Hospital Universitario de Torrejón, Madrid, Spain
Background: While the systemic inflammatory response assessed by SIRI has been recognized as a prognostic factor in advanced pancreatic cancer, understanding its association with patients’ nutritional status may provide deeper insights into disease biology and outcomes. Methods: This is an observational, non-interventional and multicenter study (15 Spanish hospitals) promoted by SEOM, including retrospective and prospectively patients with metastatic pancreatic cancer in routine clinical practice. Clinical and nutritional data was recorded, and SIRI was calculated using the formula: (neutrophils x monocytes) / lymphocytes. We considered SIRI score as low (SIRI-L) or high (SIRI-H) using a cutoff of < 2.3 or ≥ 2.3, respectively based on our previous findings. PANDORA-SEOM tool was used for electronic data collection. The main outcome is to correlate SIRI with the nutritional status. Other aims were to correlate the overall survival (OS) and progression-free survival (PFS) with SIRI and weight loss in the 3 months prior to diagnosis using the Kaplan-Meier method and multivariable Cox regression model. Data from the pilot study is presented in this abstract, and more data is expected to be available prior to the Congress. Results: We included 144 patients retrospectively 65% men, with median age of 66 years (range 45-81). The most common 1st line chemotherapy regimen were gemcitabine + nab-paclitaxel (63.2%), mFOLFRINOX (20.1%) and FOLFOX (11.8%). Prior to diagnosis, 54.2% of patients had weight loss >5 Kilograms (Kg) and 22.9% lost >10 Kg. SIRI-H was significantly associated with weight loss >5Kg compared to SIRI-L, 35.7% vs 24% respectively (p<0.029). Patients with a pretreatment SIRI-H showed shorter OS compared to SIRI-L (median OS = 12 months, Hazard Ratio (HR) 3.047, 95% Confidence Interval (CI) 2.069-4.488, P<0.001), as well as shorter PFS (median PFS 5 vs 10 months, HR 2.364, 95% CI 1.650-3.387, p<0.001). In the patient subgroup that experienced >5Kg weight loss, SIRI-H was associated with worse OS (median OS 4 vs 12 months). We didn’t find an association between CA19.9 level and SIRI or weight loss. Multivariate analysis identified SIRI as an independent prognostic factor for OS (HR 2.962, 95% CI 1.911-4.591, P<0.001). Conclusions: Our findings underscore the importance of SIRI as a significant predictor of nutritional status and disease aggressiveness in patients with metastatic pancreatic cancer. Prospective data will help us to validate these findings. Research Sponsor: Spanish Society of Medical Oncology (SEOM).

624 Poster Session
In-hospital outcomes of acute pulmonary embolism in patients with gastrointestinal cancer: A nationwide study. First Author: AJANAN POUDEL, John H. Lewis, Christian Adams-Carey, Jr. Hospital of Cook County, Chicago, IL
Background: Cancer is a well-established risk factor for the development of pulmonary embolism (PE), especially the gastrointestinal (GI) cancers. While multiple studies have reported the burden of PE in cancer patients, recent data comparing in-hospital outcomes among different types of cancer patients are lacking. This study aimed to investigate the clinical and healthcare utilization outcomes of hospitalized patients with acute PE in the context of gastrointestinal (GI) cancers. Methods: A cross-sectional study was conducted using data from the National Inpatient Sample (2016-2020). International Statistical Classification of Diseases (ICD-10) codes were employed to identify hospitalized patients admitted with primary diagnosis acute PE. Data regarding GI cancer diagnosis along with demographic information, baseline clinical characteristics, and outcome variables, including mortality, hospital length of stay, total hospital charges, complications and risk factors were collected and analyzed. Statistical analysis was performed using the survey procedures function in STATA v17, with statistical significance defined by the t-test at a significance level of p < 0.05. Results: Among the 181,060 patients admitted with primary diagnosis of acute pulmonary embolism, 550 (0.3%) had underlying gastric cancer, 1,790 (0.98%) had pancreatic cancer, 875 (0.48%) had hepatobiliary cancer, and 2,600 (1.61%) had small intestine and colorectal cancer. Mortality was found to be significantly higher in all types of GI cancer, with gastric cancer demonstrating the highest mortality rate (10%). Adjusted odds for PE, age, sex, race, payment category, comorbidities, and risk factors of PE, gastric cancer (OR 2.6, 95% CI: 1.1-6.2) and pancreatic cancer (OR 2.2, 95% CI: 1.4-3.4) were found as independent risk factors for mortality. There was no significant difference in mean length of hospital stay and mean total hospital charges in patients with or without cancer. Similarly, no significant differences were observed in complications such as requirement for mechanical ventilation, arrhythmia, cardiac arrest, need for vasopressor and thrombolysis. Conclusions: In-hospital mortality in patients with acute pulmonary embolism is significantly higher in all types of GI cancer; however, there is no significant difference in hospital length of stay and total hospital charges in patients with or without cancer. Research Sponsor: None.

625 Poster Session
Predictive machine learning models for survival outcomes in patients with pancreatic cancer. First Author: Yang-Chen Shen, Institute of Behavioral Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
Background: Identifying prognostic markers is essential for accurately assessing risk levels in pancreatic cancer patients, leading to more personalized treatment approach. In light of this, our current endeavor is to build a survival predictive model for pancreatic cancer patients using various machine learning (ML) techniques, taking into account both clinical and inflammatory factors. Methods: The research included 311 pancreatic cancer patients on a prospective basis. Their data was sourced from the Clinical Data Warehouse of National Cheng Kung University Hospital. For the purpose of predicting 6 and 12-month survival, we stratified the patients into two subgroups using a cutoff of 5Kg weight loss, SIRI-L or SIRI-H using a cutoff of $5Kg. We considered SIRI score as low (SIRI-L) or high (SIRI-H) using a cutoff of $5Kg weight loss, SIRI-L was associated with worse OS (median OS 4 vs 12 months). We didn’t find an association between CA19.9 level and SIRI or weight loss. Multivariate analysis identified SIRI as an independent prognostic factor for OS (HR 2.962, 95% CI 1.911-4.591, P<0.001). Conclusions: Our findings underscore the importance of SIRI as a significant predictor of nutritional status and disease aggressiveness in patients with metastatic pancreatic cancer. Prospective data will help us to validate these findings. Research Sponsor: Spanish Society of Medical Oncology (SEOM).

626 Poster Session
Advanced pancreatic cancer outcomes and the impact of COVID-19 pandemic: The experience of an academic cancer center. First Author: Christian Adams-Carey, University of Cincinnati College of Medicine, Cincinnati, OH
Background: The COVID-19 pandemic increased all-cause mortality and disrupted healthcare delivery in the United States. Interruptions in cancer screening and surveillance because of the pandemic resulted in delayed diagnosis, diagnosis at later stages, and worse cancer-related outcomes. However, the effect of COVID-19 on pancreatic cancer outcomes has not been reported. This study aimed to investigate this question. Methods: We studied consecutive patients with resectable and metastatic pancreatic cancer treated at the University of Cincinnati Cancer Center. Patients were grouped into two cohorts: from January 2018 to December 2019 (pre-COVID) and from January of 2020 to December of 2021 (during-COVID). Descriptive data on patient characteristics, ECOG performance status (PS), laboratory values, therapies, and mortality were obtained by pre- and during-COVID. The categorical variables were compared using the Pearson Chi-square test for contingency tables (or Fisher’s exact test when the expected frequency within any cell was less than 5 in the contingency table), and the t-test or ANOVA was used for continuous variables. For overall survival time, the Kaplan-Meier curves were compared between pre- and during-COVID using log rank test. We fitted univariable Cox proportional-hazards model for each interest variable, and the multivariable Cox models, which includes only significant variables. Results: There were 81 and 64 patients in the pre- and during-COVID cohorts, respectively. Patients diagnosed during COVID were more likely to be female, have better PS, have higher proportion of alcohol use, and were more likely to receive 5-FU-based (compared with gemcitabine-based) chemotherapy upfront. There was no overall survival difference between the two cohorts. A Cox proportional hazards model showed that PS at diagnosis, history of chronic pancreatitis, any chemotherapy compared to no chemotherapy, serum albumin prior to initial chemotherapy, and body mass index at time of diagnosis were associated with survival. Conclusions: We observed no difference in overall survival in patients diagnosed with advanced stage pancreatic cancer during the first two years of the COVID-19 pandemic compared with the two prior years. While some differences were observed between patient groups and for treatment selection before and during the pandemic, a concerted effort to maintain cancer care appears to have minimized the impact of the pandemic. Further analyses on patients undergoing treatment are being conducted. Research Sponsor: None.
Pancreatic cancer and diabetes: The effects of race and genes. First Author: Michael Shu, University of Cincinnati College of Medicine, Cincinnati, OH

Background: Pancreatic cancer and diabetes mellitus (DM) have been shown to be connected, but the genetic associations between the two have not been well characterized. The goal of this study was to identify racial and genomic patterns that relate the timing of DM onset with a pancreatic cancer diagnosis. Methods: Consecutive pancreatic cancer patients treated at the University of Cincinnati Cancer Center with available tumor genomic profiles were studied. Descriptive statistics for 133 genes, patient characteristics, cancer stage, treatment details, and family history were analyzed. Categorical variables were compared using the Pearson Chi-square test for contingency tables (or Fisher’s exact test when the expected frequency within any cell was less than 5 in the contingency table), and the t-test or ANOVA was used for continuous variables. For overall survival, we generated Kaplan-Meier curves by DM diagnosis and fit univariate and proportional-hazard models for overall survival for all patients, and multivariable Cox models, which included only significant variables. Results: Of 147 individuals with pancreatic cancer (median age 67 years, 49% female, 12% Black), 46.3% had a DM diagnosis. Of these, 62% had chronic DM, while 38% were diagnosed within one year of their pancreatic cancer diagnosis. Black individuals were more likely to have been diagnosed within a year of pancreatic cancer (69.2% vs. 30.2%, p = 0.023), compared with White individuals. There were 15 genes found to be upregulated in those with DM and pancreatic cancer, and 11 genes found to be downregulated. RNF43 mutation was more prevalent in pancreatic cancer patients with chronic DM than those without DM (71.4% vs 32.5%, p = 0.048), although absolute number of individuals with the mutation were low. No other genomic association on the timing of DM and pancreatic cancer was found. A SMAD4 mutation was associated with a 121% increased risk of developing DM (OR = 4.77, 95% CI: 1.36–15.9, p = 0.016). Conclusions: In a cohort of pancreatic cancer patients at a single center, Black individuals were more likely to have DM diagnosed at pancreatic cancer diagnosis (rather than earlier), compared to other races. No remarkable genomic associations were found. This highlights that a diagnosis of diabetes may be related to inequities in healthcare, as opposed to true genomic differences, and needs to be explored in larger datasets. Research Sponsor: None.

De-escalation and dose density in real-world patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who received FOLFIRINOX (mFFX) and modified FOLFIRINOX in the first line. First Author: Syvart Dennen, Genesis Research, Hoboken, NJ

Background: FOLFIRINOX (FFX) is a recommended first line (1L) treatment option for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who received FOLFIRINOX and modified FOLFIRINOX in the first line. First author: Syvart Dennen, Genesis Research, Hoboken, New Jersey

Methods: This retrospective observational study utilized the Flatiron Metastatic Pancreatic Cancer Enhanced Data Mart. Adult pts diagnosed with mPDAC between November 2018 and November 2022 who initiated treatment with 1L FFX in 1L within 90 days of their diagnosis for metastatic disease were included in the study. Receipt of FFX was defined as receiving all four regimen components within 90 days of 1L initiation. Modified FFX (mFFX) was defined as administration of 150mg/m2 of irinotecan or ~2720mg/m2 5-FU total (bolus+infusion) during cycle 1; doses greater than these were considered FFX. For FFX-only vs. FFX + GnP pts, median age was 66 vs. 64 (IQR: 59–71) vs. 57–69. In all analyses, we used logrank test for statistical significance. The median age at 1L initiation was 63yr vs. 65yr, 72% vs. 56% were male, 67% vs. 63% were white, 36% vs. 30% had an ECOG score of 0, 31% vs. 32% had an ECOG score of 1, and 83% vs. 81% received treatment at community oncology centers. For FXX vs. mFFX, the median age at 1L initiation was 66yr vs. 65yr, 72% vs. 56% were male, 67% vs. 63% were white, 36% vs. 30% had an ECOG score of 0, 31% vs. 32% had an ECOG score of 1, and 83% vs. 81% received treatment at community oncology centers. For FFX vs. mFFX, median OS was 11.1 months (95% CI: 9.0–15.5) vs. 4.8 months (95% CI: 4.5–5.5) (p<0.001). Among ungraded AEs, fatigue was more common in pts treated with FFX and FXX than in pts treated with mFFX (10% of pts receiving FXX vs. 25% of pts receiving mFFX; 44% FOLFIRI, 5% FOLFIRINOX, 8% 5FU + leucovorin, and 7% other (either 5FU alone or with oxaliplatin and/or irinotecan). Median 6-week dose density was 69% for 5FU (50–93%), 100% for leucovorin (66–133%), 83% for irinotecan (56–130%), and 99% for oxaliplatin (68–127%). Conclusions: De-escalation is common among pts continuing FXX treatment to mPDAC patients. Identifying predictive factors may distinguish FXX non-responders and obviate AEs. Research Sponsor: Ipsen Biopharmaceuticals, Inc.
Patterns of surgery and adjuvant therapy in pancreatic carcinoid tumor: An NCDB analysis. First Author: Connor Lanoue, Creighton University School of Medicine, Omaha, NE

Background: Pancreatic Carcinoid Tumor (PCT) is a neuroendocrine tumor (NET) of the gastrointestinal (GI) tract composed of Argentinaffin cells. Of the primary pancreatic cancers, NETs are exceedingly rare in comparison to pancreatic adenocarcinoma, accounting for less than 2% of pancreatic cancer diagnoses. PCTs constitute for only a subset of these and hold a better prognosis than adenocarcinoma (What Is a Pancreatic Neuroendocrine Tumor? American Cancer Society). Carcinoid tumors usually originate in the appendix, ileum, or rectum, and are seldom a primary neoplasm of the pancreas. PCTs generate secretory products with Serotonin being the most frequently isolated. Some cases may produce a carcinoid syndrome with characteristic diarrhea, cutaneous flushing, and bronchospasm (Ha & Tan, 2012). Surgical resection is the hallmark of this rare condition, and other modalities of management are not feasible. Due to the rarity of PCT, no significant study exists in the literature analyzing the association of survival with receipt of surgery or predictors of receipt of surgery. Methods: The National Cancer Database (NCDB) was used to identify patients diagnosed with PCT from 2004 to 2019 using the histology codes 8240 as assigned by the Commission on Cancer Accreditation program. Kaplan-Meier, ANOVA Chi-Square, Binary Logistic Regression and Cox Proportional Hazards tests were performed. Data was analyzed using SPSS version 29 and statistical significance was set at α = 0.05. Results: 2237 patients with PCT formed the final sample, with an average age of 61 years of age. 724 patients (32.3%) underwent surgery of the primary site, 72 (3.2%) received adjuvant chemotherapy, and 9 (0.4%) received adjuvant radiation. Surgery alone was associated with the longest median survival (198.5 months) compared to the other treatments (Adjuvant chemotherapy=155.3 months, Adjuvant radiation=122.7 months, No surgery=72.95 months, p<0.05). After controlling for covariates, receipt of surgery was independently associated with decreased overall mortality (HR=3.80, p<0.0001). Age, stage, lower grade tumors, and fewer positive regional lymph nodes were significantly associated with increased odds of receiving surgery. Additionally, treatment at an academic facility and private insurance status was associated with significantly higher rates of surgery. Patients who did not receive surgery were significantly older, had later stage disease, higher co-morbidity scores, and larger tumor size. Income level and race had no effect on treatment selection. Conclusions: This study found that surgery alone without adjuvant therapy is independently associated with improved survival. Favorable clinical characteristics may be contributing to this discrepancy in survival. Further exploration of treatment strategies in PCT may benefit patients through the creation of definitive treatment guidelines to manage this disease. Research Sponsor: None.

Intra-operative radiation for pancreatic cancer: Initial experience at the Hadassah Medical Center. First Author: Gianella Cornejo, Hadassah Medical Center, Jerusalem, Israel

Background: Prognosis following surgery for pancreatic cancer (PC) remains poor. Local recurrence is common and negatively impacts survival rate. In an effort to improve outcomes and improve patient survival, we have adopted a strategy of adding intra-operative electron radiation therapy (IOERT) to select patients undergoing pancreatic resection (RT) for PC. Here we report our initial experience with this treatment modality. Methods: 14 patients (10 male, 4 female), age between 44 - 81 years (mean 66.17), who underwent PR (Head 7, Body 7) between 1/2021-1/2023 were included in this analysis. Patients selected for IOERT included patients that according to surgeon assessment were at risk not to achieve satisfactory resection margins by surgery alone. All had resectable or borderline resectable disease according to standard criteria. 8 patients underwent pre-op chemotherapy followed by stereotactic body radiotherapy (SBRT) to a dose of 25-40 Gy in 5 fractions to the tumor and regional lymphatics followed by PR (5 Whipple, 3 distal pancreatoduodenectomy) and IOERT, 3 patients received neoadjuvant chemotherapy followed by SBRT only and did not undergo surgery due to tumor progression. Immediately following resection, mobile IOERT accelerator using a 40-80mm applicator with a level of 0-15 degrees was directed at the tumor bed deemed at high risk for recurrence. 10-20 Gy was delivered using 6-8 MeV electrons to the 90% isodose line at the discretion of the treating radiation oncologist. Data including serial imaging, genomic analysis, radiation protocol, complications, pathological results and outcome was collected for analysis. Results: Mean follow up was 9.7 months (2-21). 8 patients survived with no evidence of disease and 1 pt with liver metastases. 6 patients died: 4 with distant metastatic disease, 1 from disease progression prior to surgery and 1 early post-op sepsis. Negative surgical margins were achieved in 10 patients of which 2 mutated BRCA gene carriers showed complete pathological response (both who received combined neoadjuvant chemotherapy followed by SBRT). Progression free survival (PFS) was also longer in the R0 wide/CRM- group. These findings were robust with regards to grading. 5-FU based adjuvant treatment was mainly mFOLFIRINOX and show better outcome as compared to gemcitabine-based treatments. Conclusions: The present study was performed using real world data reflecting actual clinical settings. The results obtained are in good agreement with data from clinical trials, including the prognostic role of the R- and N- Status as well as the efficacy of adjuvant chemotherapy protocols used. Research Sponsor: None.
Frequency and oncologic outcomes of KRAS mutations in circulating tumor DNA of patients with pancreatic ductal adenocarcinoma. First Author: Mahmoud M.G. Yousef, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: KRAS genetic alterations have been reported in more than 90% of pancreatic ductal adenocarcinoma (PDAC). The association of KRAS mutation subtypes detected in circulating tumor DNA (ct-DNA) with survival remains unclear. We investigated the rate of liquid biopsy detected KRAS mutation subtypes, and their association with overall survival (OS) in patients with PDAC. Methods: The Foundation software platform was used to retrospectively query a single-institution electronic Health-Research Database to identify patients with PDAC who underwent ct-DNA liquid biopsy from 2018 to 2023 and extract their oncologic outcomes. Results: Liquid biopsies were performed for 313 patients with PDAC, 58% (n=181) were diagnosed with stage IV disease. The median OS from ct-DNA was 25 months, with median OS 24 months (95%CI=21-29). Overall, 52% (n=162) tested positive for KRAS mutations. Among patients with positive liquid biopsy results (n=181), 66.7% (n=120) tested positive for KRAS mutations. In contrast, only 31.8% (n=42) of patients with stage I to III disease at diagnosis (n=132) tested positive. Among patients with metastatic disease, those with KRAS positive disease had significantly shorter OS (median OS 13 vs 27 months, HR=2.7, 95%CI=1.7-4.3, P= 0.001). In patients with non-metastatic disease, the median OS was 28 vs 43 months, respectively (HR=1.7, 95%CI=0.97-2.8, P= 0.064). The most frequent KRAS mutation was G12D (66, 40.7% of KRAS mutations) followed by G12V (35.8%), G12R (35.8%), and G12C (7.4%). Positive liquid biopsy results were associated with worse OS (95%CI=1.1-3.5, P value=0.015). Conclusions: Detection of KRAS mutation in liquid biopsies of patients with metastatic PDAC is associated with worse OS. KRAS G12D/G12V alterations detection is associated with worse OS compared to other KRAS mutation subtypes. Ct-DNA detection of co-occurring CDKN2A mutation is associated with worse OS in patients with KRAS positive metastatic disease. Research Sponsor: National Cancer Institute; the Cancer Prevention & Research Institute of Texas; ASCO.

Vascular resection for pancreas cancer: Ten-year real-world experience from a single high-volume center. First Author: David Henault, University Health Network, Toronto, ON, Canada

Background: In pancreatic ductal adenocarcinoma (PDAC), to identify prognostic factors for surgically treated patients, including vascular resections. Methods: Retrospective study of 638 consecutive patients treated for PDAC at a single high-volume center (n = 715) at a high-volume cancer center. We tested associations between clinico-pathological and radiological data, perioperative therapy, time to recurrence (TR) and overall survival (OS). Results: Demographic and clinico-pathological variables were comparable to published surgical cohorts. Initial NCCN radiological staging was 533 (83%), moderate (n=198, 32%), and bad (13.7%) locally advanced PDAC. There were 467 (74.5%) resectable, 98 (13.7%) borderline, and 84 (11.7%) locally advanced PDAC. There were 467 (65.3%) pancreaticoduodenectomies, 104 (14.5%) distal pancreatectomies, and 31 (4.3%) total pancreatectomies and 112 (17.5%) aborted procedures, mostly due to metastatic disease (82.1%). Of the 603 resected cases, 351 (58.2%) were non-vascular resections (NVR), 181 (30.0%) venous-only resections (VR), and 70 (11.8%) were arterial + venous resections (AR). Median length of stay was 8 days, ICU admission rate was 6.1% (n = 37), readmissions occurred in 114 (18.8%) cases and reoperations in 47 (7.8%) cases. The 90-day mortality rate was 3.2% (n = 19) and the 5-year OS was 20.7%. Perioperative chemotherapy was given to 258 (78.4%) NVR, 129 (75.9%) VR and 60 (93.8%) AR. Perioperative chemoradiation was given to 27 (8.8%) NVR, 34 (21.0%) VR and 46 (61.5%) AR. Median TTR and OS did not significantly differ by initial NCCN staging or type of resection. Median TTR and OS were significantly shorter for VR (14.5 and 22.7 months) compared to NVR (18.6 and 30.5 months, p<0.001) and AR (20.6 months, p=0.004 and 30.9 months, p=0.017). Patients who received chemotherapy or chemoradiation had significantly longer TTR (21.0 vs. 10.2 months, p=0.001 and 25.3 vs. 16.4 months, p<0.001) and OS (21.5 vs. 17.2 months, p<0.001 and 35.5 vs. 27.5 months, p=0.030) compared to patients not receiving any therapy. In multivariate analysis, when controlling for perioperative therapy and usual clinico-pathological factors, vascular resection was not associated with TTR and OS. Perioperative chemoradiation, chemoradiation, and chemotherapy were not associated with longer TTR and OS. However, multiply co-occurring chemotherapies and/or radiation had significantly longer median and OS and (41.9 and 35.3 months) compared to patients receiving chemoradiation alone (14.3 and 24.6 months, p=0.017). Conclusion: In this cohort of patients with PDAC treated with surgical resection at a high-volume cancer center, vascular resection was not associated with oncological outcomes when controlling for administration of perioperative therapy. Research Sponsor: None.
640 Poster Session

Survival of patients with microsatellite-instability-high and Lynch syndrome-associated pancreatic ductal adenocarcinoma.
First Author: Tanish Naras, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pancreatic ductal adenocarcinoma (PDAC) remains a challenging disease due to its aggressive nature, late-stage diagnosis, and limited treatment options. There is an increased interest in cancers which harbor microsatellite instability (MSI-H) due to their susceptibility to immune checkpoint inhibitors. MSI in PDAC is rare, and little is known about survival in this subtype of pancreas cancers. Our aim was to assess overall survival in surgically resected high microsatellite instability (MSI-H), mismatch repair deficient (MMRd), and Lynch syndrome associated PDAC treated in our center.

Methods: Patients with surgically resected PDACs from 1990 to 2023 were identified. A total of 936 cases were sequenced utilizing MSK-IMPACT, a targeted next generation sequencing platform. Patients with germline or sporadic pathogenic variants or likely pathogenic variants in one of the DNA MMR genes MLH1, MSH2, MSH6, PM2S, or 5 of EpCAM were identified. MSI-H, MMRd, and LS-associated cases were matched to patients with microsatellite stable or MMR proficient, non-LS-associated PDAC in a 1:2 ratio with a direct match on age (<5 years), gender, and year of surgery (<3 years). Kaplan-Meier curves were used to visualize the data. A generalized estimating equation (GEE) Cox model with robust sandwich estimator was used to compare matched cohorts.

Results: 17 patients with MSI-H, MMRd or LS-associated surgically resected PDACs were identified. Five patients were classified as MSI-H, 3 patients were MSI- indeterminate, and 9 patients were microsatellite stable. Eight patients were found to have germline pathogenic variants in LS-associated genes. The remaining nine patients had sporadic pathogenic DNA MMR gene variants (MLH1 n=3, MSH6 n=6). Median age at surgery was 66 (interquartile range [IQR] 60-77). 41% of the patients were female, and median year of surgery was 2014. MSI-H, MMRd or LS-associated PDACs were matched to 34 control patients. The median survival time of the cases was 12 years vs. 1.9 years in the control group. Five-year survival rate was 81% (IQR 60-100%) and 18% (7.4%-43%), respectively. LS-associated, MSI-H or MMRd status in resectable PDAC was a strong predictor of good prognosis (hazard ratio 0.17, 95% CI 0.07-0.38, p value <0.001). Conclusions: MSI-H, MMRd or LS-associated PDACs displayed significantly better survival compared to their MSI-stable, MMR proficient, non-LS-associated counterparts, in the era before routine use of immunotherapy. It is expected that survival will be increased further with more frequent availability of immunotherapy. Research Sponsor: None.

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The impact of a pancreatic cancer multi-disciplinary clinic on patient-centric outcomes.
First Author: Connor Hannon, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: A one-day multi-disciplinary clinic allows for a comprehensive evaluation of patients in a single-visit format. This study aims to evaluate the impact of a one-day pancreatic cancer multi-disciplinary clinic (PMDC) on patient-centric outcomes.

Methods: Patients with pancreatic cancer who were seen at The Ohio State University PMDC from January 2021 to March 2023 were identified. Patient-centric outcomes were evaluated including time from diagnosis to first evaluation and treatment, number of coordinated appointments and visits, and diagnostic tests obtained leading up to the first treatment. Outcomes were compared to pancreatic cancer patients seen in the year prior to the opening of the PMDC (non-PMDC). Results: Among the 139 PMDC and 141 non-PMDC patients, the median number of days between referral and treatment initiation was similar (PMDC: 33 days [IQR: 22, 44] vs. non-PMDC: 32 days [IQR: 23, 42], p = 0.09). The median time between diagnosis and treatment initiation was also similar (PMDC: 28 days [IQR: 19, 37] vs. non-PMDC: 30 days [IQR: 21, 37]; p = 0.4). Of note, PMDC patients received more supportive care visits within 30 days of diagnosis (PMDC: 2 [IQR: 1, 2] vs. non-PMDC: 0 [IQR: 0, 1]; p < 0.001) and completed more visits with cancer providers (PMDC: 7 [IQR: 6, 8] vs. non-PMDC: 5 [IQR: 4, 7]; p < 0.001) compared with non-PMDC patients. In addition, PMDC patients also required fewer physical trips to the medical center (PMDC: 4 [IQR: 3, 5] vs. non-PMDC: 4 [IQR: 3, 6]; p < 0.001). Conclusions: Pancreatic cancer patients seen in a one-day multi-disciplinary clinic attend a greater number of coordinated appointments and receive more supportive care services with fewer physical trips to the medical center compared with patients not seen in a PMDC clinic. Future studies should focus on the long-term patient-centric benefits of a multi-disciplinary approach for cancer patients. Research Sponsor: None.

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Cardiometabolic risk comorbidities in exocrine pancreatic insufficiency compared to patients with cancer: A single centered observational retrospective cohort study.
First Author: James Peeples, Department of Internal Medicine, Ochsner Health, New Orleans, LA

Background: Exocrine pancreatic insufficiency (EPI) is characterized by inadequate digestion and absorption of fat and protein. EPI is associated with increased risk for pancreatic cancer as well as increased risk for diabetes and consequently cardiometabolic (CM) risk equivalents. Emerging data suggest patients with cancer also have increased CM risk equivalents. To explore the cardiovascular risk associated with both EPI and cancer, we sought to describe and compare CM comorbidities and surrogates in patients with EPI vs cancer. Methods: A retrospective observational electronic chart analysis was done at Ochsner Health, Louisiana, spanning records from January 2017-2020 comparing two cohorts: patients with EPI (n=677) and patients with Cancer (n=1432). Results: The Cancer cohort was older (65.1 ± 11.9 yrs) than the EPI cohort (54.2 ± 17.6 yrs) (p < 0.05). The Cancer cohort had higher AST levels (63.2 ± 141.2 U/L at start, 86.9 ± 247.3 U/L at end) vs the EPI cohort (50.2 ± 86.9 U/L at start, 65.4 ± 268.9 U/L at end) (p < 0.05). The Cancer cohort also had higher ALT levels (69 ± 111.4 U/L at 7-55 U/L at start, 58.5 ± 142.1 U/L at end) vs the EPI cohort (48.7 ± 79.5 U/L at start, 41.4 ± 100.3 U/L at end) (p < 0.05). No significant differences were seen in Cancer vs EPI cohort for A1C, TC, triglyceride, lipase, cholesterol, uric acid, tobacco/alcohol use, or blood pressure levels. Within the Cancer cohort, there was an increase in neuropathy (11% at the start vs 29.9% at end [p < 0.05], CHF (3.63% at the start vs 11.5% at end [p < 0.05]), and HTN prevalence (29.9% at the start vs 66.1% at end [p < 0.05]). Cancer patients also had decreased weight (175.2 ± 46.5 lbs at start, 163.8 ± 43.4 lbs at end [p < 0.05]) and BMI (27.3 ± 6.5 at start, 25.7 ± 6.4 at end [p < 0.05]). Among the general cancer cohort, no statistically different changes were seen in hypoglycemia, DKA, retinopathy, nephropathy, ESRD, dialysis, HLD, NAFLD, OSA, CAD, CVD, PAD, hyperuricemia, or gout prevalence over the period of observation or in comparison to EPI cohort. Conclusions: Patients in the Cancer cohort in this study have some indices of greater CM risk compared to those with EPI. Though older, they had significantly higher AST and ALT levels compared to EPI cohort. Over the 3 years of observation, cancer patients developed a statistically significant increase in neuropathy, CHF, and HTN prevalence, and decrease in weight and BMI. These changes may reflect consequent morbidity related both to natural disease progression and/or effects of cancer treatments such as chemotherapy. Research Sponsor: None.
The economic impact of short-term imaging with metastatic pancreatic ductal adenocarcinoma. First Author: Abbey Bayless, University of Arizona College of Medicine, Tucson, AZ

Background: Although modern cancer treatment has significantly improved overall survival, this comes with a high financial cost. Based on an NIH report on Financial Burden of Cancer Care, treating pancreatic adenocarcinoma (PDAC) costs $108K, $18K, and $125K for initial treatment, during follow-up, and in last year of life, respectively. During the course of treatment, patients will visit the hospital for acute complications for which cross-sectional imaging is obtained within 45 days of subsequent scheduled follow-up imaging. This presents an opportunity for cost saving if data could be used to identify an algorithm to avoid unnecessary duplication of imaging in a short interval. The purpose of this pilot study is to evaluate tumor growth trajectory within this short time span of 45 days to guide future trials to clarify the circumstances for which a subsequent follow up study is necessary. We retrospectively identified patients from the University of Arizona Hospital from 2016 to 2019 with metastatic pancreatic ductal PDAC (mPDAC). Subjects were included for analysis if they met the following criteria: (i) diagnosed with mPDAC; (ii) had at least 2 CT abdomen/pelvis (CTAP) within 45 days of each other with one of the studies being obtained in the emergency department; and (iii) had at least 1-3 measurable lesions as defined by RECIST 1.1 criteria. Tumor dimension was measured on axial images with the largest cross-section. For our primary outcome we used paired t-tests to evaluate the difference in mean size of all lesions (primary and metastatic). We also performed sub-group analyses comparing mean size of primary and metastatic lesions separately. An alpha level of 0.05 was used to determine statistical significance. Results: We screened 382 subjects from the tumor registry and identified 28 subjects suitable for our study. 18 subjects were female and 10 were male. We identified 69 target lesions, 23 of which were primary and 46 were metastatic. The mean sum of the largest dimension of target lesions was 2.82 cm on the initial study and 3.23 on the latter study (p<0.001). The mean sum of the largest dimension of the primary lesions was 6.62 cm on the initial study and 3.89 on the latter study (p<0.001). For metastatic lesions, the initial sum was 2.38 cm while the latter was 2.85 cm (p<0.001).

Conclusions: Our finding of increase in tumor size in 45 days for mPDAC suggests that mPDAC is aggressive and can grow even in short time span. This suggests that if the earlier study is stable or shows response, the scheduled follow-up may still be necessary to demonstrate continued stability/response. Research Sponsor: None.

Impact of facility volume on outcomes in patients with pancreatic cancer treated with radiotherapy. First Author: Arvind Rajan, The University of North Carolina, Chapel Hill, NC

Background: The impact of facility volume on overall survival (OS) outcomes in patients with pancreatic cancer (PC) treated with radiotherapy (RT), both standard chemoradiation (CRT) and stereotactic body radiation therapy (SBRT) is not well-defined. Methods: This retrospective study analyzed 16,315 patients with locally advanced (LA) or borderline resectable (BR) PC from the National Cancer Database (2004-2019) who received neoadjuvant RT or RT without surgery across RT facilities with low (<10 cases/yr), intermediate (10-20 cases/yr), and high-volumes (>20 cases/yr) of PC cases. Log rank and cox regression were used for univariable and multivariable survival analysis, and Kaplan-Meier curves were generated. Results: Patients were largely treated at low (n=8055) volume centers, followed by intermediate (n=3783), and high (n=4477). Approximately half of the cohort were male (51.4%), and predominantly white (82.5%), and non-Hispanic (92%). On univariable analysis (Table), high-volume centers had improved survival outcomes in the overall population, as well as in both SBRT and CRT subsets (p<0.0001). On multivariable analysis, treatment during the most recent time period: 2016-2019 (HR 0.64, p<0.001), receiving care at a high-volume center (HR 0.84, p<0.001), use of SBRT (HR 0.91, p<0.001), administration of multigiant chemotheraphy (HR 0.706, p<0.001) and undergone surgical resection (HR 0.405, p<0.001) were associated with improved OS. In a subgroup analysis of patients receiving SBRT, median OS was 22.6 months for high-volume, 20.0 for intermediate-volume and 18.4 months at low-volume centers (p<0.001). Conclusions: Patients receiving RT for LACP or BRPC at high-volume centers had longer OS compared to those receiving RT at low-volume centers. This suggests that there may be a benefit to receiving SBRT at high-volume centers had improved OS compared to intermediate- and low-volume centers. These findings suggest that radiation oncologists’ expertise is critical for providing high-quality RT in PC, especially for SBRT. Research Sponsor: None.

Early results of a pancreas cancer learning health network: Canopy Cancer Collective. First Author: Joseph M. Herman, Northwell Health Cancer Institute, Lake Success, NY

Background: Pancreas cancer (PC) is the third leading cause of cancer death in the United States. Canopy Cancer Collective (CCC) was founded in 2019 given the urgent need for better care for patients and patient/caregiver experience. The goal of the CCC is to create an inclusive of patients, 14 care centers formed a learning health network (LHN) to share best practices: 1) quality improvement coaching, 2) topical workgroups, 3) peer workgroups, 4) working to expand to additional populations and settings, 5) a community platform for documentation and collaboration. Methods: In October 2022, LHN representatives gathered to establish aims for the year. Inclusive of patients, 14 care centers formed a learning health network (LHN) to share best practices: 1) quality improvement coaching, 2) topical workgroups, 3) peer workgroups, 4) working to expand to additional populations and settings, 5) a community platform for documentation and collaboration. Results: Through a consensus process, the LHN arrived at four aims to achieve by December 31, 2022: 1) patients from our tumor registry from 2016 to 2019 who were diagnosed with metastatic lesions separately. An alpha level of 0.05 was used to determine statistical significance. Results: We screened 382 subjects from the tumor registry and identified 28 subjects suitable for our study. 18 subjects were female and 10 were male. We identified 69 target lesions, 23 of which were primary and 46 were metastatic. The mean sum of the largest dimension of target lesions was 2.82 cm on the initial study and 3.23 on the latter study (p<0.001). The mean sum of the largest dimension of the primary lesions was 6.62 cm on the initial study and 3.89 on the latter study (p<0.001). For metastatic lesions, the initial sum was 2.38 cm while the latter was 2.85 cm (p<0.001).

Conclusions: Our finding of increase in tumor size in 45 days for mPDAC suggests that mPDAC is aggressive and can grow even in short time span. This suggests that if the earlier study is stable or shows response, the scheduled follow-up may still be necessary to demonstrate continued stability/response. Research Sponsor: None.

A qualitative exploration of perceptions and experiences towards physical activity among patients with pancreatic ductal adenocarcinoma undergoing treatment. First Author: Tyra Nguyen, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Patients with pancreatic ductal adenocarcinoma (PDAC) experience significant symptom burden due to the disease and its treatment, thus limiting their ability to engage in physical (PA) and social activities. In addition to the physical and psychosocial benefits, and exploring its value and how to deliver it to patients with PDAC could support their health and well-being. Therefore, the objective of this qualitative research was to explore perceptions and experiences of PA among PDAC patients undergoing active treatment. Methods: Qualitative semi-structured interviews were conducted with individuals with PDAC. Participation was voluntary among individuals in the DigiSTEPS prospective trial evaluating associations between PA measures, performance status, and patient-reported outcomes (NCT03757182). Interviews were conducted virtually. Data were analyzed using inductive thematic analysis. Results: Ten patients (50% male, 80% white, mean age=70 years) participated in the interviews. While clinical approaches may often be informational and seek to educate PDAC patients regarding the importance of PA and the benefits of PA participation, findings suggest that participants understand the benefits of PA and are interested in being active. However, cancer symptoms and treatment-related side effects are substantial barriers that are hard to surmount. A further barrier was the dissonance in self-perceptions, particularly the contrast in their functional abilities and body composition pre- to post-cancer diagnosis. We identified four action items to support patients in overcoming these barriers: clinicians can leverage trust in their team to provide evidence-based information on how to be active; distribute wearable activity monitors which can increase motivation; harness virtual PA opportunities during more symptomatic periods; and provide PA trainers with cancer knowledge to tailor programming. Conclusions: This research highlights the importance of tailoring PA discussion and approaches based on a PDAC patient’s phase in the cancer survivorship continuum, their stage at diagnosis, and treatment type. In addition, clinical teams and trainers should consider patient concerns related to body image and develop programs that meet their needs. Further research is needed to develop effective interventions integrating access to counseling psychologists to address these concerns and promote PA in positive and adaptive ways. Clinical trial information: NCT03757182. Research Sponsor: Internal CSMC Funding. Pancreatic Cancer Action Network.
Trials.gov: NCT04098432. The study was financially supported by Bristol-Meyer-Squibb.

Conclusion: Combination chemotherapy with oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) showed improved survival compared to gemcitabine mono-
therapy for patients with metastatic pancreatic cancer and has become the one of the standard regimens. Despite of its clinical benefit, FOLFIRINOX needs continuous infusion of 5-FU for 46 hours, which removes patient’s quality of life. In other metastatic cancer, infusion pump free regimens, in which oral 5-FU drug replace the continuous infusion of 5-FU, have developed as alternative regimens by its convenience. Therefore, we planned to develop new combination chemotherapy with oxaliplatin, irinotecan, and S-1 (OX-IRIS) for metastatic pancreatic cancer. Methods: HGCGS1803 study has conducted as a randomized, single arm, phase II study in Japan. The chemotherapy-naive patients with metastatic pancreatic cancer were eligible. S-1 (40 mg/m²) orally intake twice daily for 14-day followed by a 14-day rest, and intravenous 65 mg/m² of L-
OHp and 100 mg/m² of irin 1 day and 15 days every four weeks were continued until disease progression or unacceptable toxicity. The primary endpoint was objective re-
sponse rate (ORR) by RECIST ver.1.1, with a threshold of 10% and an expected value of 30%. The secondary endpoints were overall survival (OS), progression-free survival (PFS), and safety. Results: Between Jan 2020 and May 2022, forty patients were enrolled and 39 patients included in full analysis set (one patient was excluded because of consent withdrawal). Median age was 66 (range, 41-75), female/male were 16/23, ECOG PS 0/1; 22/7, UGT1A1 wild/heterozygous for *6 or *2 allele 27/12, liver/lung/pancreatic me-
tastasis 28/9/11, respectively. The median relative dose intensities of S-1, irinotecan, and oxaliplatin were 76%, 72%, and 70%, respectively. Objective response rate and disease control rate were 43.6% (95% CI 27.8-60.4%) and 76.5% (95% CI 60.4-89.1%), respectively. In median progression free survival and overall survival were 4.3 months (95% CI 2.5-6.2 months) and 11.9 months (95% CI 7.2-14.9 months), respectively. Four patients discontinued protocol therapy due to adverse events (AE) without disease progression. Grade 3 or higher AE were observed in 15 patients (15%). Hyponatremia (15%), lymphopenia (11%), leucopenia (11%), anemia (11%), peripheral neuropathy (10%), ALT elevation (10%), AST elevation (9%), anorexia (8%), nausea (8%), febrile neutropenia (5%). One patient died due to protocol therapy (drug induced pneumonitis). Conclusions: OX-IRIS showed high response rate with manageable safety, and the primary endpoint was met. This new triplet regimen could be a useful first line therapy option for patients with metastatic pancreatic cancer. Clinical trial information: JICTD01119008. Research Sponsor: None.

Stereotactic radiotherapy plus anti PD-1 therapy in patients with locally advanced unresectable pancreatic cancer: Results from a phase 1/2 clinical trial (CA209-9KH). First Author: Milan Vosmik, University Hospital Hradec Králové, Hradec Králové, Czech Republic. Background: The outcomes after the treatment for pancreatic ductal adenocarcinoma (PDAC) have not improved. Except for MSI high tumors, PDAC is considered to be resistant to immune checkpoint inhibitors (ICI). Radiotherapy is thought to be a potential option to foster the effect of ICI. This investigator-initiated trial evaluated safety and efficacy of combining stereotactic radiotherapy (SRT) and ICI. Methods: In this open-label, multicenter phase 1/2 study, patients (pts) aged ≥ 18 years with histologically confirmed metastatic PDAC were eligible. Patients were randomized to the treatment arms: 1) antroquinonol (AQ) 80 mg/m², gemcitabine (Gem)/nab-paclitaxel (Nab-P) 100 mg/m² and IT dose escalation (dose escalation range 120 to 250 mg/m² and cycle 4 dose 100 mg/m²),; 2) Gem/Nab-P 100 mg/m², IT dose escalation (dose escalation range 120 to 250 mg/m² and cycle 4 dose 100 mg/m²),. Treatment duration was 12 months. First dose escalation was performed with a 10% increase of antroquinonol. The second dose escalation was performed with a 50% increase of antroquinonol. Treatment duration was 12 months. First dose escalation was performed with a 10% increase of antroquinonol. The second dose escalation was performed with a 50% increase of antroquinonol. A total of 52 patients were enrolled from 20 institutions in Japan, and a total of 101 regimens were administered. Concomitant collagen diseases included rheumatoid arthritis (n=35), systemic lupus erythematosus (n=5), Sjögren’s syndrome (n=4), vasculitis syndrome (n=3), dermatomyositis/polymyositis (n=2), poly-
ymyalgia rheumatica (n=1), systemic sclerosis (n=1), and Behcet’s disease (n=1). The most common regimen for pancreatic cancer was gemcitabine/nab-paclitaxel (Grp, n=40), S-1 monotherapy (n=18), gemcitabine monotherapy (n=15), modified FOLFIRINOX (n=10), S-1 concurrent radiotherapy (n=5), and FOLFIRI (n=4). Treatment discontinuation due to AEs occurred in 21 regimens (20.8%). The most common causes of discontinuation were thrombosis in 4 regimens, interstitial lung disease (ILD) in 3 regimens, and fatigue in 3 regimens. Infection as an adverse event was observed in 7 regimens (6.9%). Grp had the highest discontinuation rate for adverse events of 37.5% and an incidence of ILD of 15.0%. The median PFS was 5.6 months in first-line therapy, and the median OS was 11.1 months. By regimen, the median PFS (5.8 months) and median OS (13.3 months) for metastatic patients receiving first-line Grp were comparable to those in previous reports on Grp for patients without collagen disease. Patients with metastatic pancreatic cancer concomitant with collagen disease have a high discontinuation rate due to AEs, and attention should be given to the occurrence of thrombosis and ILD. Research Sponsor: None.
Pharmacogenomic study of gemcitabine on the safety and efficacy in patients with metastatic pancreatic cancer (GENESECT study): Analysis of subpopulation. First Author: Takashi Yokokawa, Department of Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: In the GENESECT study, we examined the relationships between gemcitabine (GEM) metabolism-related germline genetic polymorphisms (GPs) and treatment efficacy and safety. However, no significant GPs were found because approximately 70% of the patients were treated with nab-paclitaxel, which has a different metabolic process than GEM. In the present study, a subanalysis including only GEM monotherapy patients was performed. Methods: Of the 159 patients analyzed in the GENESECT study, only the GEM monotherapy patients were selected. The endpoints were the carbohydrate antigen 19-9 (CA19-9) response (reduction $\geq 50\%$ from the pretreatment level at 8 weeks), progression-free survival (PFS), and overall survival (OS) in relation to GPs from the viewpoint of efficacy, and neutropenia $\geq$ Grade 3 and thrombocytopenia $\geq$ Grade 3 in relation to GPs from the viewpoint of safety. The analyzed genes included those encoding GEM transporters and metabolic enzymes (SLC22A1, ABCBS, CDA, DCK, RRMI1/2), and a tumor cell proliferation enzyme (COX2). Statistical analysis included univariate and multivariate logistic regression analyses. The significance level was set to $5\%$. Results: Data of 50 patients were analyzed. A homozygous GCC genotype in ABCBS 1146A$\rightarrow$G (rs7639610) was associated with a significantly higher percentage of CA19-9 responses compared to AG/GG (92.9% vs 21.2%, $p = 0.023$), and the association remained significant on multivariate analysis (OR: 6.255, $p = 0.014$). Patients with AA genotype in ABCBS 1146A$\rightarrow$G tended to be associated with PFS, but this was not statistically significant (HR: 0.464, $p = 0.074$). On the other hand, there was no significant association between ABCBS 1146A$\rightarrow$G and CA19-9 response, however, the number of patients was too small to draw a conclusion. TT/CT genotype in DCK 1205C$\rightarrow$T was significantly associated with prolonged PFS compared to CC (median, 127 vs 48 days, $p = 0.002$), and the association remained significant on multivariate analysis (HR: 0.153, $p = 0.028$). No GPs were significantly associated with OC, and the presence of second-line chemotherapy was the only relevant factor. In terms of safety, no GPs were significantly associated with either neutropenia or thrombocytopenia. Conclusions: The results suggest that ABCBS and DCK might be related to the efficacy of treatment with GEM, but further research is needed. Clinical trial information: UMIN000012720. Research Sponsor: None.

Anlotinib plus chemotherapy as first-line therapy for patients with gastrointestinal tumor with unresectable liver metastasis: Updated results from a multi-center, multi-phase II trial ALTERT-G-001-cohort C. First Author: Junwei Wu, Department of Oncology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Advanced gastrointestinal (GI) tumors, such as colorectal, gastric and pancreatic cancers (CRC, GC, and PC), and esophageal squamous cell carcinoma (ESCC), 20%-50% with liver metastases (LMs) have a poor prognosis. Previous trials showed that anlotinib as induction therapy. After induction therapy, 4 patients (1 PC, 2 GC, 1 BTC, and others), the median age was 64 years (34-74), 63.4% were male (NC). In cohort C (29 PC, 6 GC, 5 BTC, and others), the median age was 64 years (34-74), 63.4% male, 92.7% ECOG PS 1 and 56.1% had LMs only. The majority of the pancreatic cancer patients (26/29) received gemcitabine plus paclitaxel chemotherapy combination with anlotinib as induction therapy. After induction therapy, 4 patients (1 PC, 2 GC, 1 BT) received surgical resection. Of 37 evaluable patients in cohort C, ORR and DCR were 45.9% and 86.5% (PR, n=17; SD, n=15; 12 SD had reduced tumor size). Of 25 evaluable pancreatic cancer patients, 12 had PR, 10 had SD, ORR and DCR were 48% and 88%. According to the Kaplan-Meier method, the median DoR was 4.2 months (95%CI). The median PFS was 5.5 months (95%CI, 4.7–6.3). 37 patients in cohort C had TEAEs and $\geq$ grade 3 TEAEs (51.2%) mainly included neutropenia (19.5%), white blood cell decreased (12.2%), and blood platelet decreased (9.8%). Conclusions: Anlotinib plus chemotherapy, anlotinib plus monotherapy has proven both efficacy and safety, and might be a favorable option for advanced LMs GI tumors, especially for pancreatic cancer. Clinical trial information: NCT02562335. Research Sponsor: None.

Neoadjuvant SBRT plus regional nodal irradiation with concurrent capecitabine for patients with resectable pancreatic cancer: Survival analysis of a prospective phase 1 trial. First Author: Mustafa Basree, Department of Human Oncology, University of Wisconsin–Madison, Madison, WI

Background: Radiation may have a role in management of patients with early-stage pancreatic cancer. However, the role of regional nodal irradiation (RNI) is not well defined despite the high frequency of occult nodal disease. The goal of this trial was to evaluate the safety and feasibility of stereotactic body radiation therapy (SBRT) to primary disease with RNI, combined with capcitabine as a neoadjuvant approach for resectable pancreatic cancer. The principal survival analysis will be presented here. Methods: This is a prospective, single institution, phase IB/II dose-escalation trial that enrolled patients with biopsy-proven, resectable, pancreatic adenocarcinoma between 2014 – 2019 (NCT1918644). Patients were enrolled into one of the 3 cohorts with escalating dose levels. Neoadjuvant SBRT to the primary tumor was delivered in 5 fractions of 5.6, 7 Gy with concomitant capcitabine. All patients received RNI 5 Gy x 5 fractions. Our initial report found no dose-limiting toxicities (Witt et al IJROBP 2020). Clinico-pathologic features were summarized using descriptive statistics. Kaplan-Meier curves were employed for survival analysis. Results: Seventeen patients were enrolled on the protocol with sixteen evaluable (94%). Thirteen (76.5%) patients proceeded to surgery. Median follow up was 31.1 months (2.0 – 73.2). Among the evaluable patients, 63% were male, median age at diagnosis was 73 years (63 – 84), pre-treatment CA 19-9 149.5 U/mL (2.0 – 19358.0). The majority of patients had CT2-3 (94%) and C0 (87.5%) disease. In patients who underwent resection, median time from radiation to surgery was 19.7 days (14.8 – 42.4), with a median of 18 lymph nodes removed (11 – 27). Pathologically involved nodes were present in 63.2% of patients and a median of 2 nodes (1 – 10). Five patients (31.3%) received neoadjuvant chemotherapy, and ten (62.5%) received adjuvant chemotherapy. At the time of data cutoff, median overall survival was 31.1 months (2.3 – 73.6), and median locoregional control and distant metastasis free survivals were 32.8 months (4.0 – 59.5) and 15.3 months (0.4 – 73.6), respectively. No significant GPs were associated with OS, and the presence of second-line chemotherapy was the only relevant factor. Conclusions: Neoadjuvant chemoradiation with SBRT and capcitabine to primary disease with RNI is feasible and provided a promising signal of durable local control in our study, despite high rates of pathological nodal involvement. Further investigation of this strategy is warranted in a larger cohort of patients. Clinical trial information: NCT1918644. Research Sponsor: None.
Results of a phase II, open-label pilot study evaluating the safety and activity of liposomal irinotecan (NAL-IRI) in combination with S-FU and oxaliplatin (NALIRFOX) in preoperative treatment of pancreatic adenocarcinoma (NCT 01856257). First Author: Thomas J. George, UF Health Cancer Center, Gainesville, FL.

Background: Neoadjuvant treatment for resectable pancreatic cancer (PDAC) is increasing in acceptability, but a standard regimen has yet to be established. The modified FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen often requires dose modifications, delays and growth factor support due to toxicity. Liposomal irinotecan injection (NAL-IRI) is FDA-approved with a well-tolerated safety profile in relapsed, refractory mPDAC. This current study substitutes NAL-IRI for traditional irinotecan in the mFOLFIRINOX regimen (NALIRFOX) and aims to demonstrate safe neoadjuvant delivery. NALIRFOX is currently under review by the FDA for frontline mPDAC.

Methods: This phase 2, open-label, multicenter single-arm study enrolled adult patients (pts) with operable PDAC, resectability (borderline vs. resectable) confirmed by multidisciplinary care, adequate organ function, and ECOG performance status (0-1). Pts received NALIRFOX (per NAPOLI-3) every 2 wks x 4 mo followed by repeat imaging and surgical resection 4-8 wks later. Primary endpoint is the composite 30 day post-op major complication rate (hospital re-admission, death, second surgery, procedure or major complication extending hospital stay). A sample size of 25 pts will detect a 20% reduction in 1st endpoint (from 30% to 10%; 1-sided exact test; α=0.05; β=0.8). Toxicity, treatment completion, R0 resection, clinical, biochemical and radiographic response rates and QOL during treatment (FACT-G) are 2nd endpoints. Serial microvessel specimens have been collected for exploratory analysis.

Results: From May 2019 to Feb 2023, 45 pts were enrolled from 4 centers. Median age was 63 (41-76), majority women (53%), white (89%) with borderline (n=30) or resectable (n=15) disease. All 45 pts initiated treatment with 34 proceeding to surgery and 29 completing definitive resection. Most common grade 3 AEs included non-hematologic neutropenia (41%), diarrhea (30%), and anemia (22%). Those not obtaining definitive resection had progressive disease (radiographic n=6; intra-n=5), physician change of tx (n=2); toxicity (n=2; CMV colitis and TPN requirement/ sepsis) or consent withdrawal (n=1). Three (10%) pts had a post-op major complication (p=0.012). One pt died from post-op bleeding complications. Resections included both borderline (n=15) and resectable (n=14) initial disease with overall R0 resection rate of 89%.

Conclusions: Neoadjuvant NALIRFOX was safe, having met the primary study objective, with reasonable rates of treatment completion and surgical outcomes for this relatively high-risk group of pts. Additional analyses are ongoing and will be reported at the meeting.


The interim analysis of a single-arm, open-label, phase II study investigating ALLEN regimen (durvalumab plus albumin paclitaxel and lenvatinib) in patients with metastatic pancreatic cancer (mPC). First Author: Meixia Chen, Department of Bio-therapeutic, The First Medical Center, Chinese PLA General Hospital, Beijing, China.

Background: Metastatic pancreatic cancer is a leading cause of cancer death worldwide with limited treatment options. Durvalumab, the anti-PD-L1 inhibitor has revealed remarkable efficacy in solid malignancies including hepatobiliary cancers. We conducted a study to evaluate the efficacy and safety of a combination therapy of Durvalumab, Albumin paclitaxel and Lenvatinib (ALLEN Regimen) in patients with mPC.

Methods: This open-label, single-center, single-arm, phase II clinical trial investigated patients with metastatic pancreatic cancer. Durvalumab (1000mg IV, q3w), albumin paclitaxel(180-220 mg/m² IV q3w) and lenvatinib (8mg PO qD) were given regularly until disease progression. The primary endpoint was objective response rate (ORR) evaluated by investigators according to RECIST 1.1. The secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and treatment-related adverse events (TRAEs). Results: Between September 2021 and September 2023, seventeen patients with ECOG score 0-2 were enrolled, including 8 patients (47%) who were refractory to at least one systemic chemotherapy. The median follow-up was 6.0 months (95% CI 4.0-8.4). 17 patients were evaluable, with a median age of 58 years. 9 patients (52.9%) were male. The DRR and DCR were 64.7% and 94.1% respectively. The median PFS was 7.9 months (95% CI 3.1, 11.4), and the median OS was 8.1 months (95% CI 4.7, 13.5). TRAEs (all grades) occurred in 16 (94.1%) patients. The most common grade 1-2 TRAEs were nausea 8 (47%), diarrhea 5(29.4%), peripheral sensory neuropathy 3 (17.6%) and hypertension 3 (17.6%). No grade 3 or higher TRAEs occurred. Conclusions: The ALLEN regimen demonstrated promising antitumor activity and well acceptable toxicity in metastatic pancreatic cancer. Further randomized controlled trials will be required in a larger patient population. Clinical trial information: NCT05327582. Research Sponsor: None.

Incorporating stereotactic body radiation therapy for inoperable pancreatic cancer. First Author: Alexander Lukez, Fox Chase Cancer Center, Philadelphia, PA.

Background: The management of inoperable pancreatic cancer (PC) is controversial. We sought to determine local progression (LP) rates are high among patients with inoperable PC. SBRT for inoperable PC provides reasonable local control. Early SBRT reduces the need for LP before death compared with late SBRT. Further investigation into the role of SBRT for inoperable PC is necessary. Research Sponsor: None.

Preliminary results of a phase II study of surufatinib plus sintilimab, nab-paclitaxel and gemicitabine (AG) as first-line therapy in patients (pts) with locally advanced or metastatic pancreatic adenocarcinoma (mPDAC). First Author: Dong-Sheng Zhang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, National Clinical Research Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China.

Background: Advanced pancreatic adenocarcinoma (PDAC) had poor survival and limited therapeutic options. Surufatinib is a potent, small-molecule tyrosine kinase inhibitor (TKI), selectively targeting VEGF receptors (VEGFR) 1, 2, and 3, FGFR 1 and CSF-1R. Recent studies showed that small molecule anti-vascular inhibitor combined with a PD-1 inhibitor demonstrated promising efficacy for PDAC. This study is to assess the efficacy and safety of surufatinib plus sintilimab (an anti-PD-1 antibody),nab-paclitaxel and gemicitabine(AG) as first-line therapy for mPDAC pts. Here we report the preliminary results.

Methods: Eligible pts ≥18 years old with histologically confirmed mPDAC, ECOG PS 0-1, with at least one measurable lesion were enrolled. Pts received surufatinib (250mg, orally daily), sintilimab (200mg, I.V., D1, Q3W), nab-paclitaxel (125mg/m², I.V., D1, D8, Q3W) and gemicitabine (1000mg/m², I.V., D1, D8, Q3W). Baseline cumulative incidence functions showed that death without LP favored early vs late SBRT (p = 0.099). Additionally, death without LP favored early vs late SBRT (p = 0.011). Conclusions: LP rates are high among patients with inoperable PC. SBRT for inoperable PC provides reasonable local control. Early SBRT reduces the need for LP before death compared with late SBRT. Further investigation into the role of SBRT for inoperable PC is necessary. Research Sponsor: None.

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Does metformin use effect overall survival for patients with pancreatic cancer? First Author: Ravi Ramjeesingh, Division of Medical Oncology, Nova Scotia Cancer Center, Dalhousie University, Halifax, NS, Canada

Background: In Canada, the incidence of pancreatic cancer ranks 11th amongst all cancers but has resulted in the third highest mortality. Despite advancements in both diagnostics and therapeutics, the 5-year overall survival rate of pancreatic adenocarcinoma (PDAC) remains under 10%. Emerging studies have begun to examine the role of the hypoglycemic medication metformin, in improving outcomes of patients with PDAC.

Methods: We conducted a retrospective study of 630 patients diagnosed with PDAC treated at the Halifax Infirmary and Health Science Centre. Patients were included if they were ≥ 19 years of age at time of diagnosis and had a minimum follow-up of 1 year. Patients were excluded following randomization or death prior to the initiation of therapy. Metformin use was defined as any prescribed dose of the medication for at least one month prior to diagnosis. The primary endpoint was overall survival (OS) from diagnosis to death. Chi-square tests were used to compare categorical variables, and the log-rank test was used for survival comparisons. The study cohort was compared to a national database of PDAC patients (Canada's Cancer Registry).

Results: Among the 630 patients identified, there were 337 males and 293 females. The average age at time of diagnosis was 74.02 years. There was no significant difference found in overall survival of patients on metformin (n=132, mean overall survival (mOS) 6.68 months), compared to those not on metformin (n=498, average survival 7.44 months, p=0.989). Further subgroup analysis based on cancer stage showed that patients with resectable pancreatic cancer (AJCC stage I/II, n=149), who did not use metformin (n=106) had a mOS of 12.98 months compared to 9.71 months for metformin users (n=34), p=0.438. For patients with locally advanced disease (AJCC stage II-B-III, n=125), the average mOS of non-metformin users (n=103) was 11.10 months compared to 10.73 months for metformin users (n=22), p=0.803. For patients with pancreatic cancer (AJCC stage IV, n=365), the average survival of non-metformin users (n=289) was 3.48 months compared to 4.26 months for metformin users (n=76), p=0.803. Diabetic patients (n=195) on metformin (n=132) compared to those not on metformin (n=63), did not show significant survival difference (mOS 6.68 months vs 6.61 months respectively, p=0.602). Conclusions: Despite the limitations of this observational study, we found no statistically significant improvement in mOS for metformin use in PDAC patients. Future research including a prospective study should be undertaken to confirm these results in a larger sample size.

Research Sponsor: None.

Non-responders to neoadjuvant chemotherapy in pancreatic adenocarcinoma: Characteristics and outcomes. First Author: Brenda Harrington, Department of Surgical Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: For patients with localized pancreatic adenocarcinoma, resection and systemic therapy remain the mainstays of curative-intent treatment. Neoadjuvant chemotherapy is commonly employed for patients with high disease early and improving patient selection for surgery. Those who do not respond to neoadjuvant therapy present a challenge with a lack of randomized data to aid in decision making. Here we sought to define the characteristics and outcomes of those patients to guide clinical practice.

Methods: This was a single-institution retrospective cohort study using a prospectively maintained database of those diagnosed with pancreatic adenocarcinoma. Patients included in the study were those who received neoadjuvant chemotherapy. Non-responders were defined as those with both no radiographic and no biochemical response at the first re-assessment after initiation of therapy.

Results: A total of 176 patients were identified who were treated with neoadjuvant chemotherapy with curative intent. Of those, 42 (23.8%) patients had no evidence of either radiographic or biochemical response. Of those patients, 14 were upfront resistant (33.3%) and 20 were borderline resectable (47.6%). An additional 8 (19%) were locally advanced. Most patients received FOLFIRINOX as a first line chemotherapy agent (n = 25, 59.5%). A total of 12 (28.6%) patients underwent neoadjuvant radiation therapy. A total of 19 (45.2%) proceeded to surgery and two of those who were found to be unresectable at exploration, resulting in 17 (40.5%) who ultimately received curative-intent resection. Exactly half (n = 21) of the patients had their chemotherapy switched (CS). Of those who had CS, 11 (52.4%) had evidence of local tumor progression on their initial restaging scan compared to just 3 (14.3%) of those who did not (p = 0.02). Additionally, patients who had CS had higher incidence of vascular involvement on their initial scan (90.5% vs 52.3%, p = 0.051). A total of 6 (26.8%) who underwent CS had subsequent biochemical response compared 4 (19.0%) of those who did not. Ultimately, 6 (26.8%) of those who had CS ultimately proceeded to surgery compared to 12 (61.9%) of those who did not (p = 0.062). Interestingly, there was no significant difference in median overall survival between those who had CS (18.6 months) and those who did not (19.9 months, p = 0.525).

Conclusions: Non-responders to frontline neoadjuvant systemic therapy present a clinical challenge and have poor rates of curative-intent resection. Chemotherapy switch was employed mostly in cases with worse prognostic factors and thus infrequently lead to resection. Despite this, it may be important in certain overall survival situations in which the survival of those who did not respond to front line chemotherapy.

Research Sponsor: None.

A phase II study of maintenance rucaparib in patients with platinum sensitive, advanced pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2 or PALB2. A four year survival update. First Author: Kim Anna Reiss, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA

Background: We previously reported the results of a single arm, phase II study of maintenance rucaparib in patients with advanced, platinum-sensitive pancreatic cancer and pathogenic germline or somatic variant in BRCA1, BRCA2 or PALB2 variants (Reiss et al, JCO, 2021). We now report the five year follow-up of this trial.

Methods: Patients with advanced, platinum-sensitive pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2 or PALB2 were enrolled in this single arm phase II study performed at the Abramson Cancer Center. Patients were required to have received ≥ 16 weeks of platinum-based treatment without evidence of platinum resistance, which was defined as growing lesions, new lesions or steadily rising tumor markers. Chemotherapy was discontinued and patients received rucaparib 600mg PO BID until progression, unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall response rate (ORR), disease control rate (DCR) and overall survival (OS).

Results: Of 42 evaluable patients, seven (17.6%) remain progression-free for over four years (5 BRCA2, 1 BRCA2, 1 PALB2) of whom four (9.5%) have been progression-free for five years. Two of these four patients discontinued rucaparib due to adverse events after three and four years of therapy, respectively, without signs or symptoms of progression to date. At the cutoff date, we observe an mPFS 12.9 months, mOS 24.3 months, DCR 41.6% (9 PRs, 6 CRs), noting that three patients converted from partial to complete response since our prior publication. Two patients with ongoing responses succumbed to treatment-related toxicity. One patient had a PFS of 2.6 years with disease progression at 2.6 years as a cause of death.

Conclusions: Here we report the four year progression-free survival rate of maintenance rucaparib in patients with BRCA1 or PALB2-related pancreatic cancer. Our data suggest that selecting patients for this particular treatment may achieve highly durable clinical remissions. This finding is further highlighted by two patients who have discontinued rucaparib for adverse events one and two years ago, respectively, and have not had biochemical or imaging evidence of progression to date. Given the cost and risk of treatment-related leukemia associated with PARP inhibition, this data highlights the need to better understand the highly variable biology of patients with PC and BRCA or PALB2 variants, and raises the possibility of whether a very small, select group may be cured by PARP inhibitors.

Clinical trial information: NCT03140670. Research Sponsor: Clovis Oncology, Basser Center for BRCA.

Phase II study of the safety and efficacy of discontinuing pegfilgrastim for pancreatic adenocarcinoma treated with FOLFIRINOX. First Author: Masahiro Yanagi, Department of Gastroenterology, Kanazawa University Hospital, Kanazawa, Japan

The original FOLFIRINOX regimen (S-fluorouracil, leucovorin, irinotecan, oxaliplatin) for metastatic ductal adenocarcinoma of the pancreas (PDAC) is associated with a high risk of febrile neutropenia (FN), and pegfilgrastim has been used to reduce the risk. However, it remains unclear how long pegfilgrastim needs to continue. This study evaluated the safety and efficacy of FOLFIRINOX after discontinuing pegfilgrastim in PDAC patients.

Methods: This prospective phase II trial included patients with PDAC who completed the first three courses of FOLFIRINOX, with ongoing pegfilgrastim prophylaxis for FN, and did not experience FN. The patients continued on FOLFIRINOX without pegfilgrastim from the fourth course. The primary endpoint was development of FN. The secondary endpoints included relative dose intensity (RDI), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The threshold and expected development of FN were 20% and 7%, respectively, at a one-sided significance level of 0.10 and statistical power of 80%. Based on this hypothesis, we calculated the number of patients needed to be 33. Results: In total, 34 patients (20 male, median age 66 years) were enrolled from August 2017 to September 2021. Twenty-three patients were unresectable, and 11 were borderline resectable. FN developed in one patient. Grade 4 neutropenia was observed in six patients, grade 3 neutropenia in 10 (29.4%), anemia in four (11.8%), diarrhea in two (5.9%), and malaise, lung infection, peripheral sensory neuropathy, colitis, and biliary tract infection in 1 (2.9%) each. Twenty-two patients required dose reduction, mainly because of neutropenia. Mean RDIs at the sixth course of oxaliplatin, leucovorin, fluorouracil, and continuous infusion of fluorouracil were 77.0%, 88.2%, 81.8%, 84.4%, and 87.6%, respectively. ORR, median PFS, and median OS were 44.1%, 15.8 months, and 25.8 months, respectively.

Conclusions: FOLFIRINOX can be continued safely with a low incidence of FN after discontinuing pegfilgrastim in PDAC patients who did not experience FN during the first three courses of FOLFIRINOX, if the drug dose is reduced appropriately for neutropenia from the fourth course. Clinical trial information: UMIN00002085. Research Sponsor: None.
Postoperative complications following neoadjuvant therapy and surgery in a phase 2 borderline resectable pancreatic cancer clinical trial (Alliance A021501).

Background: Postoperative complications in patients with borderline resectable pancreatic cancer treated with neoadjuvant therapy and pancreatectomy in the national cooperative group setting have not been previously characterized. Further, the impact of preoperative hyperfractionated radiotherapy on postoperative outcomes is largely unknown. We sought to quantify perioperative morbidity among patients with pancreatic cancer who received neoadjuvant modified FOLFIRINOX chemotherapy and prefrontal hyperfractionated radiotherapy on a multicenter clinical trial. Methods: The A021501 phase 2 trial randomized patients with borderline resectable pancreatic ductal adenocarcinoma to 8 doses of mFOLFIRINOX (Arm 1) or 7 doses of mFOLFIRINOX then hyperfractionated radiotherapy (Arm 2), followed by pancreatectomy (Dec 31, 2016-Jan 1, 2019). Patients underwent resection according to defined operative standards at enrolling centers without specific requirements for either surgeon or hospital volume. Surgical complications and adverse events were assessed and captured at a single time point of 90 days after surgery and compared between treatment arms. Results: Of 126 enrolled patients, 51 (40%) underwent pancreatectomy (n=32, Arm 1; n=19, Arm 2) at 28 institutions. Vascular resection was performed in 19 patients (37%). One patient in Arm 2 died within 90 days after surgery. Rates of any surgical complication were 19% (n=6) in Arm 1 and 42% (n=8) in Arm 2 (p=0.07). Median length of stay was 7 days (range 5-38 days). Five (10%) patients required reoperation within 90 days. Readmission rates were higher in Arm 2 than Arm 1 (16% vs. 4%, p=0.04) but there were no differences in rates of reoperation, pancreatic fistula or abscess requiring drainage, or wound infection between study arms. 54% of patients (n=26/48) experienced a grade 3 or higher adverse event, with no difference between treatment arms (47% vs 68%, p=0.7). Rates of initiation of adjuvant therapy did not differ between treatment arms (66% vs. 68%, p=0.4). Pancreatic fistula and abscesses were associated with adjuvant therapy (p<0.001). No differences were observed based on occurrence of surgical complications (HR 1.1; 95% CI 0.5-2.6). Conclusions: In this national cooperative group study of patients with borderline resectable pancreatic cancer, postoperative complications following neoadjuvant chemotherapy, radiation, and surgical resection were common. Although complications were mild to moderate, high-volume institutions with prior experience and using large datasets. Multimodality trials of preoperative therapy for locoregionally advanced pancreatic cancer may be safely performed in the cooperative group setting. Clinical trial information: NCT02839343. Research Sponsor: NIH/NCI/NCI; NIH/NIN/H/NCI; NIH/NIN/H/NCI.

Results of the safety and tolerability of ivaltinostat plus capecitabine in the phase 1b portion of a phase 1b/2, dose-escalation, randomized, multi-center study in the maintenance (maint) setting in patients with metastatic pancreatic adenocarcinoma (mPDAC). First Author: Evan Justin Walker, University of California, San Francisco, CA

Background: The standard of care for patient (pts) with advanced or mPDAC typically consists of mFOLFIRINOX or gemcitabine/nab-paclitaxel used in the front-line setting until disease progression (pro) or toxicity. A tolerable maint therapy (tx) that can effectively delay disease progression while preserving quality of life with minimal cumulative toxicity is highly desirable. Ival, an orally available prodrug (deacetylation) inhibitor that increases histone acetylation (HA), suppresses PDAC cell proliferation, and promotes apoptosis in PDAC cell lines. Preclinical data demonstrated synergy with 5-FU/capecitabine in mouse models. The phase 1b study will determine an optimal combination of ival and cap in combination with high-volume institutions and using large datasets. Multimodality trials of preoperative therapy for locoregionally advanced pancreatic cancer may be safely performed in the cooperative group setting. Clinical trial information: NCT040140672. Research Sponsor: Arcus Biosciences; Gilead Sciences.

References:
- Pancreatic cancer may be safely performed in the cooperative group setting. Clinical trial
- datasets. Multimodality trials of preoperative therapy for locoregionally advanced pancreatic cancer may be safely performed in the cooperative group setting. Clinical trial information: NCT02839343. Research Sponsor: NIH/NCI/NCI; NIH/NIN/H/NCI; NIH/NIN/H/NCI.

Conclusions:
- Combination therapy of ival with cap has shown clinical promise in phase 1b/2 trials and has been well tolerated and the safety and PK/PD data support a RP2D of ival of 250 mg/m2.

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Factors associated with the receipt of surgery in acinar cell carcinoma of the pancreas. First Author: Jasleen Kaur Chaddha, Creighton University School of Medicine, Omaha, NE

Background: Acinar cell carcinoma of the pancreas (PACC) accounts for 1% of adult pancreatic tumors. Clinically, this malignancy presents as a hypersecretory syndrome as lipase is released into circulation. Median overall survival is 18 to 47 months. Aggressive surgical resection is associated with long-term survival in PACC patients. This appears to be the treatment of choice for most localized pancreatic cancers, however, there are no clear treatment guidelines or standardized protocols for PACC due to its rarity. Further, no significant study has analyzed the factors correlated with receiving this surgery. This study aims to uncover the possible factors associated with the receipt of tumor resection in patients with PACC. Methods: The National Cancer Database (NCDB) was used to identify patients diagnosed with PACC from 2004 to 2019 using the histology code 8550 as amended by the Commission on Cancer Accreditation program. Kaplan-Meier, ANOVA Chi-Square, and Multilevel Logistic Regression were performed, and data were analyzed using SPSS version 29. Statistical significance was set at α = 0.05. Results: 1430 patients with PACC were queried. 600 (41.95%) patients received surgical resection. Surgical patients experienced longer overall survival than non-surgical patients (87.5 months vs. 25.3 months, P < 0.001). Of the surgical patients, wider surgical margins and complete tumor resection were associated with improved survival (P < 0.001). Stage I and II disease, well and moderately differentiated disease, and receiving treatment at an academic/research facility were associated with an increased likelihood of receiving surgery (P < 0.001). Metastasis at the time of diagnosis was associated with a decreased likelihood of receiving surgery (P = 0.001). Income status, insurance status, and age did not appear to be significant predictors of surgery. Of the initial sample, 219 (15.31%) patients received adjuvant chemotherapy, 8 (0.55%) patients received adjuvant radiation therapy, and 4 (0.28%) patients received both adjuvant chemotherapy and radiation therapy. Adjuvant therapies did not appear to impact the overall survival of PACC patients. Conclusions: This study confirms that tumor resection is associated with increased survival in patients with PACC. Improved survival with surgery is correlated to wider surgical margins and complete tumor resection. It appears that patients with well or moderately differentiated disease, stage I or II disease, and treatment at an academic/research facility are more likely to receive surgery. PACC patients with metastasis distant sites are less likely to receive surgery. The role of adjuvant therapy remains unclear. Further studies are needed to better understand the factors involved in receiving surgery and other treatment modalities as part of PACC treatment. Research Sponsor: None.

PRIMUS-002: A multicentre, open-label, phase II study examining FOLFOX and nab-paclitaxel (PA) and nab-paclitaxel and gemcitabine (AG) as neo-adjuvant therapy for (borderline) resectable pancreatic cancer (PC), focusing on biomarker and liquid biopsy development. First Author: Derek B. Grose, University of Glasgow, Glasgow, United Kingdom

Background: There is increasing evidence suggesting benefit from a neoadjuvant approach to PC. However, the optimal regimen is unclear and will likely require a precision medicine approach. Platinum-containing regimens have shown survival benefit for PC, but are associated with exceptional toxicity. Biomarker and liquid biopsy-defined treatment and decision treatments are often based on patient performance status (PS) and co-morbidity. Tumors may show defective DNA damage response (DDR), conferring potential selective sensitivity to DNA damaging agents (e.g. platinum) and newer targeted agents. We have shown that DDR deficiency (DDRd) is present in up to 25% of PC. This study is designed to exploit DDRd as a therapeutic vulnerability, validated using tissue and liquid biopsy to define candidate BM for FA and AG response. Methods: Patients with resectable and borderline resectable PDAC patients who were deemed fit for potential surgery were recruited into the trial between April 2019 and July 2021. All had been molecularly profiled using the Precision-Panc Cancer Clinical Genome including a novel DDRd assay, and the transcriptome with longitudinal sampling (pre-, during, and post-treatment). Patients received either FA (nab-paclitaxel 150mg/m² IV, oxaliplatin 85mg/m², folinic acid 35mg flat dose, fluorouracil infusion 2400mg/m² continuous IV infusion), or AG (nab-paclitaxel 125mg/m², gemcitabine 1000mg/m²) for 3 months, based on patient age and PS. The primary endpoint was disease progression (DP) during neoadjuvant therapy. Results: 31 patients in total were recruited into the trial unfortunately the trial was terminated early due to funding issues. The median age was 62 years old (31-71) 21 patients were male and 10 female. 7 resectable cases and 24 borderline resectable at diagnosis were included in this study. Patients were randomized 1:1 to receive either FOLFIRINOX plus HIFU and continued chemotherapy or AG. This protocol was initiated due to extent of malignancy The overall median survival time was 20.6 months with a 90% confidence interval of (12.9 months to 24.9 months). The median survival time was 23.7 months with 90% confidence interval of (12.6 months to 24.9 months) for FOLFIRINOX-A, and 20.5 months with a 90% confidence interval of (8.9 months to NA) for the AG arm. Conclusions: We have demonstrated that these 2 regimes can be utilised in the neoadjuvant setting with surgery being undertaken safely following therapy (there was no surgical mortality and morbidity in line of other international series). Further work is ongoing to identify potential biomarkers which may lead to better patient selection for a neoadjuvant approach. Clinical trial information: ISCRN34129115. Research Sponsor: CRUK; BMS/Celgene.

FOLFIRINOX plus high intensity focused ultrasound for locally advanced/ borderline resectable pancreatic ductal adenocarcinoma: A prospective single arm phase II trial. First Author: Dong Ho Lee, Department of Radiology, Seoul National University Hospital, Seoul, South Korea

Background: FOLFIRINOX has been the standard regimen for locally advanced pancreatic cancer. Therefore, there were the efficacy and safety of FOLFIRINOX plus HIFU for neoadjuvant treatment. According to the results of animal studies, concurrent use of high intensity focused ultrasound (HIFU) and chemotherapy can enhance the drug delivery to the target tissue. In this phase II trial, we aimed to evaluate the safety and therapeutic efficacy of FOLFIRINOX plus HIFU for patients with LAPC or BRPC.

Methods: This study was designed as a prospective single center randomized phase II study. The trial was conducted at Seoul National University Hospital in Seoul, South Korea. A total of 20 patients were enrolled. As previously reported, 6 pts were enrolled in phase 1b and RP2D was determined to explore the efficacy and safety of surufatinib combined with immunotherapy. Study identifier: NCT05262452. We prospectively enrolled 60 patients (35-85 years old, median age 67.0 years old) with LAPC (n=23) or BRPC (n=37). The median tumor size was 4.0 cm (Interquartile range, 2.7-4.6). All patients were treated by FOLFIRINOX (oxaliplatin, 85mg/m² of body-surface area; irinotecan, 180mg/m²; leucovorin, 400 mg/m²; and fluorouracil, 400 mg/m² given as a bolus followed by 2400 mg/m² given as a 46-hour continuous infusion) every 2 weeks until disease progression. HIFU was combined in the first 4 cycles of chemotherapy with following parameters: intensity of 2.0 kw/cm², duty cycle of 1%, exposure time of 3 minutes and PRF of 10Hz. Follow-up contrast enhanced CT was taken every 4 cycles for the response evaluation using response evaluation criteria for solid tumor 1.1. Overall survival (OS) and progression-free survival were estimated using Kaplan-Meier method. All analyses were intention-to-treat.

Results: Two patients withdrew the consent, and two patients could not complete planned 4 cycles of FOLFIRINOX plus HIFU treatment owing to sepsis from severe neutropenia related to chemotherapy. Among 56 patients who completed the 4 cycle of FOLFIRINOX plus HIFU and continued chemotherapy, partial response was achieved in 36 patients (60.0%, 36/60), and stable disease in 20 patients. Regarding the adverse effect (AE), 32 of 60 patients experienced grade 3 (n=22) or grade 4 (n=10) AE, all of them were related to FOLFIRINOX chemotherapy. No AE related to HIFU was observed. The estimated OS was 94.8%, 75.9% and 67.6% at 6-, 12- and 18-months respectively. Regarding the OS, 5-year overall survival was 75.6%, 7.8% and 0% at 1-year, 2-year and 3-year respectively. Conclusions: FOLFIRINOX plus HIFU was safe and effective treatment for LAPC/BRPC, providing 60.0% of partial response rate without any additional AE to chemotherapy. Clinical trial information: NCT05262452. Research Sponsor: None.
Biweekly gemcitabine plus nab-paclitaxel as first-line therapy for older adult patients with unresectable pancreatic cancer: A prospective study. First Author: Kenji Ikezawa, Department of Hepatobiliary and Pancreatic Oncology, Osaka International Cancer Institute, Osaka, Japan

Background: Although the number of older adult patients (aged ≥ 75 years) with pancreatic cancer (PC) is increasing, there are still limited data regarding chemotherapy for these patients, who experience adverse events more frequently than younger patients with PC. In this study, we evaluated the efficacy and safety of biweekly gemcitabine plus nab-paclitaxel (GnP) as first-line therapy for older adult patients with unresectable PC. Methods: We conducted a single-center, prospective study. Patients aged ≥ 75 years with pathologically proven unresectable pancreatic adenocarcinoma were enrolled after obtaining written informed consent. Patients were treated with a modified regimen of gemcitabine (1000 mg/m²) and nab-paclitaxel (125 mg/m²) on days 1, 15 of every 28-day cycle. The primary endpoint was the overall response rate. Secondary endpoints included disease control rate, overall survival, progression-free survival, 1-year survival rate, 2-year survival rate, and adverse events. Results: From August 2018 to March 2021, 17 patients were enrolled (locally advanced 4, metastatic 13). Five patients (29.4%) were men, and the median age was 77 years (range: 75-81). The median Geriatric 8 score was 13 points (range 6-17). Biliary drainage was performed in 7 patients in the overall population. The overall response rate was 47.1% (8/17). Disease control rate was 82.4% (14/17). Median overall survival was 16.8 months (95% confidence interval (CI) 5.9-24.6) and median progression-free survival was 8.3 months (95% CI: 4.9-10.1), respectively. The 1-year survival rate and 2-year survival rates were 58.8% and 29.4%, respectively. Grade 3 or 4 hematologic adverse events and non-hematologic adverse events were observed in 17.6% (3/17) and 29.4% (5/17), respectively. No deaths was observed in association with biweekly GnP regimen. Conclusions: Biweekly GnP as first-line therapy can provide favorable treatment outcomes with tolerable toxicity in older adult patients with unresectable PC. Clinical trial information: JRCTs051190038. Research Sponsor: None.

674 Poster Session

Comparison between different therapeutic sequences in patients affected by metastatic pancreatic ductal adenocarcinoma. First Author: Andrea Pretta, Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy

Background: The first-line treatment of metastatic pancreatic cancer involves different therapeutic regimens, among them, mFOLFIRINOX and gemcitabine-nabpaclitaxel. Herein, we report a common control which includes a cross-over to a second line chemotherapy, following a second-line non-cross-resistant chemotherapy (gemcitabine or fluorouracilimide-based combinations). Survival distribution was assessed by Kaplan-Meier curves. The primary endpoint was median overall survival. Statistical analysis was performed with MedCalc package. Results: The median age was 66 (± 9), 195 (54.4%) were male and 163 (45.6%) were female. 292 (81.5%) patients start gemcitabine plus nabpaclitaxel as first line treatment, while 66 (18.5%) patients start mFOLFIRINOX first-line therapy. No statistically significant differences in terms of mOS were observed between the two mFOLFIRINOX and gemcitabine-nabpaclitaxel groups: 16 versus 15 months, respectively, p=0.2). No significant differences were found in terms of mPFS either: 7 versus 8 months, respectively, p=0.3). Conclusions: The results of our retrospective study showed no statistically significant survival advantage between the sequences starting with mFOLFIRINOX or with gemcitabine-nabpaclitaxel. Further studies will be necessary to establish the effectiveness of new therapeutic schemes to be introduced into clinical practice in order to define a better therapeutic algorithm. Research Sponsor: None.

675 Poster Session

Precision Promise (PrP) Bayesian platform trial for metastatic pancreatic cancer (mPDAC): Results of the first experimental arm, SM-88 as second line therapy. First Author: Paul Eliezer Oberstein, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: PrP is a phase 3 Bayesian adaptive platform trial for efficiently testing multiple treatments in cancer. It operates through a common control. All arms which sequence into a common control have a fixed randomization stage 1, which allows for a consecutive open label stage 2. All arms with a common control which sequence into a control arm end in a fixed randomization stage 2. The maximum size of an arm is 40 patients. All statistical measures in PrP are Bayesian. Superiority (HR < 1) is assessed monthly and is claimed should the Bayesian probability of benefit be ≥ 98%. Futility analyses occur monthly once 50 subjects have accrued to the arm. Accrual ends for futility if Bayesian predictive power (PP) of eventual success in PrP is < 20% for all the arm’s signatures. Follow-up continues for 12 months after arm accrual stops. PP experimental arm designs are flexible: an arm’s protocol appendix can supersede the master protocol. However, type I error is controlled at < 0.025, as shown by simulation. Results: SM-88 entered PrP in Apr 2020. As the first experimental arm in PrP, it was randomized 7:3 against control arms. Pooled controls for SM-88 were gemcitabine-nabpaclitaxel and mFOLFIRINOX at standard doses, since no other therapy was a backbone for SM-88. Between 4/2020 - 10/2021, 142 subjects were screened, 73 subjects started therapy and are included in the mITT cohort. 55 subjects were enrolled in the SM-88 arm and 18 in control arms. Median age was 65, 41% were female and 67% had ECOG-0. As per protocol, accrual stopped at its first futility analysis in Nov 2021 based on Predictive power (PP) 0.0001 (see table), which is less than the protocol bound 0.20. SM-88 toxicity was mild. Interim results at accrual stop and final results (12 month follow up) shown below. mOS was 4.1m for SM-88 vs 8.1m for control. Conclusions: Leveraging small sample sizes of SM-88 and controls, arm’s randomization in PrP was compellingly evidenced SM-88 futility in 2nd line mPDAC. SM-88 concluded to assess other therapies, utilizing time-adjusted, as well as concurrently randomized, controls. Clinical trial information: NCT04229004. Research Sponsor: Pancreatic Cancer Action Network; Tyme Technologies, Inc.
Stereotactic body radiotherapy compared to conventionally fractionated radiotherapy for locally advanced or oligometastatic pancreatic cancer. First Author: Ofri Mizrahi, Hadassah Hebrew University Medical Center, Jerusalem, Israel

Background: Pancreatic cancer, particularly in its locally advanced and oligometastatic forms, poses a formidable therapeutic challenge. Radiotherapy remains an important treatment in an attempt to gain local control, however there is no consensus on whether stereotactic body radiotherapy (SBRT) is appropriate as compared to conventionally fractionated radiotherapy (CFRT). Herein, we report our experience.

Methods: We conducted a retrospective analysis of patients with locally advanced and oligometastatic pancreatic cancer who received definitive radiotherapy at our institution between January 2010 and March 2023 with SBRT 30-50 Gy in 3-5 fractions or CFRT 50-60 Gy in 25-30 fractions. We excluded all patients with resectable disease who underwent surgery. Clinicopathological data, treatment regimens, and radiation parameters were collected and analyzed. Results: A total of 51 patients (17 females, 34 males; median age: 67.9 years) were treated with CFRT, and 27 patients (52.9%) were treated with SBRT. Median time of follow-up for the entire cohort was 14.4 months. A total of 13 patients (25%) experienced a Local failure (LF) at a median time of 18.5 months, with no difference observed between CFRT and SBRT groups. Cancer-specific mortality (CSM) was statistically significant with a lower mortality rate in SBRT (37%) vs CFRT group (63%).

Significant treatment characteristics and dosimetric factors such as sex, age, receipt of chemotherapy, type of chemotherapy, use of elective nodal irradiation, GTV size, biologically equivalent dose (BED) corrected prescribed dose, minimum dose to GTV, or max dose to GTV did not predict local failure. There was no difference in QOL and toxicity between the two groups. Conclusions: In our cohort, local failure rates remain high and were similar between patients treated with SBRT compared to those treated with conventionally fractionated radiotherapy. We were unable to identify any specific predictors for local recurrence in this patient population. Our observation of a lower CSM rate among patients who received SBRT needs further study. The findings underscore the need to further improve radiotherapeutic approaches in an attempt to improve local control in locally advanced disease. Research Sponsor: None.

Prognostic factors for GEM + nab-PTX combination therapy in elderly patients with pancreatic cancer. First Author: Kazuki Watabe, Chiba University Hospital, Chiba, Chiba, Japan

Background: Japanese Clinical Practice Guidelines for Pancreatic Cancer 2022 recommends gemcitabine (GEM) + nab-paclitaxel (nab-PTX) therapy (GnP regimen) as the first line chemotherapy for elderly patients with pancreatic cancer. In Japan, it is reported that about 69% of pancreatic cancer patients are elderly, and only few groups reported the safety of GnP regimen. In this study, we investigated the anti-tumor efficacy and prognostic factors of GnP regimen in patients with pancreatic cancer at our hospital, with a particular focus on age.

Methods: 163 patients who started GnP therapy as the first line treatment for unresectable pancreatic cancer between February 2016 and December 2021 were included in the study. 70 years of age or older was defined as elderly, and patient background and treatment efficacy were compared in two groups: non-elderly patients (n=84) and elderly patients (n=79). Prognostic factors were also compared between the overall population and the elderly. Results: Patients with a primary lesion in the pancreatic head were 32 (38.1%) of the non-elderly patients and 35 (46.1%) of the elderly patients. 60 patients (71.4%) of the non-elderly and 38 (50.0%) of the elderly had distant metastases. The median overall survival was 16.0 months for the non-elderly and 17.7 months for the elderly, with no significant difference (p=0.93).

Significant prognostic factors for the overall subject population were ECOG PS (HR 1.80, p<0.019), liver metastasis (HR 2.36, p<0.01), SRP (HR 1.91, p<0.01) and NLR (HR 2.65, p<0.01). The only significant prognostic factor in the elderly was liver metastasis (HR 2.59, p<0.01). Conclusions: GnP regimen in pancreatic cancer can be expected to have the same antitumor effect in elderly patients as in non-elderly patients. However, significant prognostic factors were reduced in the elderly, we need to identify specific factors to determine the indication for treatment in the elderly patients. Research Sponsor: None.
A transcriptomic approach to explore the immune landscape of patients with pancreatic ductal adenocarcinoma with prognostic impact. First Author: Jonathan Antonio Lopez Guerrero, Instituto Valenciano de Oncología (Ivam), Valencia, Spain

**Background:** Pancreatic ductal adenocarcinoma (PDAC) is characterized by its immunologically cold tumor microenvironment (TME) with scarce T cell infiltration and few molecular signatures of immune activation. To date, the immunotherapies including the immune checkpoint blockade of PD-1 and CTLA-4 either single or in combination have shown modest results in PDAC tumors. Recently, the Lymphocyte Activation Gene (LAG3) has emerged as a promising checkpoint target as indicated by preclinical and clinical data. The aim of this study is to explore the immune profile of a series of PDACs and to evaluate its prognostic impact. **Methods:** A 5-mm thick section of Formalin-Fixed Paraffin-Embedded (FFPE) tissue from a retrospective cohort of 28 PDAC cases were analyzed using the Precision Immunooncology panel (PIP, HTG Molecular Diagnostics) on a NextSeq 550 sequencer (Illumina). The RNA expression of 1392 immune-related genes were analyzed. Principal Components (PC) and Manhattan distance were studied for data visualization and clustering. Maxstat algorithm (maxstat v0.7-25) was used to establish optimal cut-offs for variable categorization. Log-rank and Cox regression were used for both univariate and multivariate for survival. All tests were two-tailed. The statistical analysis was performed using R studio (R version 4.0.3). Lastly, immuno-histochemistry (IHC) for CD4, CD8, CD20, PD1, PD-L1, and LAG-3 proteins was performed on tissue microarrays (TMAs) to assess their correlation with RNA expression.

**Results:** Unsupervised analysis of the gene expression identified two clusters of patients with differentially prognostic information. These two groups were defined with a logistic regression model of 14 genes (BTLA, CXCR5, DLX, KLHDC9, KRT2, LAG3, LGALS3, PDCD4, PDCD10, PDCD11, PDCD13, PDCD14, RNF2, and SPN). The RNA expression of cluster 2 was a median survival of 13 (97.583) and 57 (6.275-26.08) months, respectively (p-value = 0.0088). This predictive model was independently validated in the PDAC dataset of the Cancer Genome Atlas (TCGA) (p<0.0001). Interestingly, cluster 1, was characterized by a significant overexpression of genes which level changed in a reverse manner compared to the next immune checkpoint (IC) receptor target. Moreover, Cluster 1, exhibited the overexpression of other such ICs such as PD1, PD-L1, IDO1, LIF and CTLA4, defining cluster 1 as an immunologically hot TME. IHC for LAG3 and other ICs showed a moderate correlation with HTG results. **Conclusions:** In this study, a prognostic transcriptomic signature of 14 genes was identified and validated using digital pathology. This signature clearly identifies two prognostic groups that could constitute the basis for tailored immunotherapy with specific IC inhibitors. LAG3 is a promising target for immunotherapy in PDAC patients. Research Sponsor: H2029- FETOPEN-2018-2019-2020-01 Contract no: 899708.
Molecular characterization of small extracellular vesicles in patients with pancreatic cancer treated with neoadjuvant chemotherapy followed by stereotactic body radiation therapy (SBRT).

**Background:** Currently, pancreatic cancer (PanC) is one of the serious gastrointestinal diseases, and more than 90% of the patients die within five years of diagnosis. Therefore, to improve PanC-related mortality, new therapeutic and diagnostic/prognostic measures are urgently needed. In this study, we examined the usefulness of plasma small extracellular vesicles (sEV) to discover molecular biomarkers associated with treatment response and overall survival from the plasma samples collected on a prospective clinical trial assessing the efficacy of SBRT following chemotherapy in pancreatic cancers (NCT03660023).

**Methods:** PanPatients (n=22) with locally advanced and borderline inoperable disease were recruited at the University of Alabama Comprehensive Cancer Center. They were administered either FOLIRINOX (5-FU, folinic acid, oxaplatin, and irinotecan) or paclitaxel (gemcitabine-paclitaxel) for 2 months followed by SBRT (33 Gray in 5 fractions). The primary objective of this single-center pilot study was to evaluate the safety and tolerability of this treatment regimen. Further, blood was collected at baseline and, at the end of chemotherapy and radiotherapy, sEV were isolated from archived plasma samples by an established ultracentrifugation method and characterized for size and concentration by nanoparticle tracking analyses (NTA), shape and size by transmission electron microscopy (TEM), and surface expression of exosomal tetraspanin markers (CD63, CD9, and CD81) and a PanC marker (CA19-9) by nano-flow cytometry. Lastly, sEV in longitudinal plasma samples were characterized for the expression of specific PanC-related miRNAs (mir196a-5p, mir155-5p, mir-21, mir-1246, and mir-34a-5p) by qPCR (RT-PCR).

**Results:** Neoadjuvant FOLIRINOX and gemcitabine-paclitaxel followed by SBRT were safe and well tolerated by most patients. NTA data showed that the ultraconcentrification method yielded highly pure sEV (with average diameter of ~200 nm) from archived baseline and longitudinal plasma samples. TEM analysis further confirmed the shape and size of the isolated sEV. Nano-flow cytometry showed the expression of exosomal markers, CD63, CD9, and CD81, as well as PanC marker CA19-9 on the surfaces of sEV. The expression of various PanC-related miRNAs in sEV was heterogenous and correlated with corresponding clinical parameters, including treatment response and overall survival. Neoadjuvant chemotherapy in combination with SBRT is safe and tolerable regimen to treat patients with locally advanced and borderline PanC. Further, sEV in the plasma of PanC patients could serve as useful prognostic and predictive markers.

**Conclusions:**
- **Clinical outcomes and molecular characteristics of patients with pancreatic acinar cell carcinoma.** First Author: Cody Estlinger, Department of Internal Medicine, Mayo Clinic Arizona, Phoenix, AZ
- **Background:** PACC is a rare malignancy originating from the exocrine pancreas, accounting for less than 1% of all pancreatic cancers. Due to the rarity of the disease entity, limited numbers of data to develop effective treatment decisions. This retrospective analysis of BRPC, LAPC, and medically inoperable PDAC patients to evaluate ALC changes after A-RT and the potential association with spleen dose in this setting.
- **Methods:** Pathology records from Mayo Clinic (AZ, FL, MN) patients (pts) denoting acinar or mixed-acinar cell carcinoma were searched between 2002 to 2023 and selected for retrospective review. Pt demographics, treatment courses, and next best therapy options for significant number of pts. In addition, more than one-third of the pts harbored targetable alterations in RAF, HRD, and MMR genes, offering additional therapeutic options for significant number of pts. In addition, more than one-third of the pts harbored germline mutations in HR genes. Therefore, somatic and germline testing should be considered for any pt diagnosed with PACC.

**Research Sponsor:** None.
The prognostic value of mutational signatures in pancreatic cancer. First Author: Nicholas Light, University of Toronto, Toronto, ON, Canada

Background: Pancreatic ductal adenocarcinoma (PDAC) is associated with poor overall survival (OS), however there are significant outliers. Understanding the biological factors driving PDAC cancer may reveal new biomarkers and treatment strategies. Mutational signatures, imprinted in the cancer genome, encode the life history of the cancer and may be used to stratify tumors into clinically-relevant subgroups. Methods: In this study we performed mutational signature analysis (MutationPatterns, COSMIC v3.3) on whole genomes from 434 PDAC patients, comprising 167 patients with resected primary tumors, and 267 advanced PDAC from patients enrolling in the COMPASS trial. We evaluated whether the mutational signatures detected associate with OS using the log-rank test in the overall cohort and stratified by disease stage, adjusting for multiple hypotheses with 5% false discovery rate (FDR). We further characterized these associations in exploratory analyses. Results: Among the 55 COSMIC signatures detected in the overall cohort, the presence of three signatures significantly associated with OS after FDR correction. SSBS5, a signature associated with indirect effects of activation-induced cytidine deaminase, was present in 18/434 (4.1%) samples, and was significantly associated with improved OS in the overall study population (log-rank p=6.5e-4, FDR-adjusted p=0.0026). SSBS9, a signature of unknown etiology previously seen in other gastrointestinal cancers, was present in 4/434 (0.9%) samples, and was significantly associated with worse OS in the overall study population (log-rank, p=7e-6; FDR-adjusted p=0.012). Conclusions: We identified three mutational signatures—SSBS5, SSBS9, and SSBS3—have not previously been described in PDAC and associate with OS. Further characterization of these novel signatures in PDAC and their underlying biology may uncover new treatment avenues. Research Sponsor: None.

Genomics and transcriptomics of pancreatic adenosquamous carcinoma. First Author: Brooke Elizabeth Kania, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ

Background: Pancreatic cancer (PC) is anticipated to become the 2nd leading cause of cancer-related deaths by 2030. Pancreatic adenosquamous carcinoma (PASC) is a rare subtype of PC with biology including squamous adenomatous features (~30% squamous histology), while pancreatic squamous cell cancer (PSCC) consists purely of squamous cells. We evaluated genomic, transcriptomic and prognostic differences between PASC, PSCC and pancreatic ductal adenocarcinoma (PDAC). Methods: Study cohort includes 501 PC tumors (83 PASC, 22 PSCC & 846 PDAC) plotted at Carci Life Sciences with WTs (Illumina, Novaseq) and NextGen DNA sequencing (NextSeq, 592 genes and NovaSeq, WES) and IHC were analyzed. Immune cell fraction was calculated by QuantiSeq. Overall survival (OS) analysis (time of tissue collection to last contact) was obtained from insurance claims and calculated with KM method. Statistical significance was determined using Chi-square/Fisher-Exact and adjusted for multiple comparisons (q<0.05). Higher infiltration of CD4+ T cells into the TME was seen in PASC vs PDAC (non-zero %, 73% vs 57%, p=0.012). There was increased OS for PASC compared to PSCC (12.6 vs 4.7 mo, p=0.015). Conclusions: Standard therapy and biomarkers are needed for PASC. A potential new biomarker for PASC is the presence of squamous differentiation genes (5 vs 2%, p=0.012). Associated with worse OS only in the resected cohort (log-rank, p=2.3e-4, FDR-adjusted p=0.012)

Mucin 5 AC (MUC5AC) to predict pathologic treatment response (TR) to neoadjuvant chemotherapy (NAT) in resected-pancreatic ductal adenocarcinoma (R-PDA). First Author: Ashish Manne, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: MUC5AC is a gel-forming glycoprotein that exists in two major glycosylations in PDAC. We studied the differential expression and predictive value of heavily glycosylated mature MUC5AC (MM) detected in the apical (Ap) and/or extracellular region (EC) and less-glycosylated immature MUC5AC (IM) detected only in the cytoplasm (Cyt) in R-PDA. Methods: R-PDA formalin-fixed paraffin-embedded tissue blocks from January 2016 to August 2021 were obtained from the Ohio State University call. Immunohistochemistry was performed to study the expression for MM and IM using monoclonal antibodies 45M1 and CLH2, respectively, and H-scores were calculated. Analysis of variance (ANOVA), t-tests, and Wilcoxon tests were used for statistical analysis. Results: Tissue samples from 100 R-PDA (43 received NAT and 57 had upfront surgery) (ups) were available for testing. There were 70 males (91%) and 30 females. MM and IM were positive in 96% R-PDA (MM-95% Ap and 72% Ec). In the NAT group, 89% (n=38) had 5-fluorouracil (5FU) based 2 FOLFOX, and the rest received gemcitabine (Gem)-based therapy; patients received a median of 6 cycles of NAT; 37% (16) had neoadjuvant chemoradiation (CRT) after NAT; 63% (27) had adjuvant systemic therapy (AST); pathologic objective response (OR = near complete or partial) and no response (NR) to NAT was reported in 63% (27) and 37% (16), respectively. In Ups group, 92% and 4% had AST (48 Gem-based, 4 IMU-based) and adjuvant CRT, respectively. The median time to recurrence (mTTR) and overall survival of the group was 15 and 23 months (m), respectively. NAT group had significantly (p<0.05) lower EC-positive MM (mean H-score 108 vs. 131), IM (mean H-score 122 vs. 162), and mTTR (11 vs 15 m) than Ups group. IM levels were directly proportional to the response (near complete (mean H-score 98) < partial (105) < NR (152) < Ups (162), p=0.04). Other TR results are discussed in the table. Conclusions: MUC5AC (IM > MM) is a potential predictive marker for TR among PDAC patients, specifically among those receiving FOLFOXIRI. These associations must be validated in further prospective studies. Research Sponsor: IRP, Pelotonia
Outcomes in patients with pancreatic and ampullary carcinoma whose tumors harbor pathogenic APC mutations. First Author: Christopher Pishvaian, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD.

Background: APC (adenomatous polyposis coli) is master regulator of the WNT signaling and beta-catenin pathway. Pathogenic (path) mutations in APC are well known for their connection to familial adenomatous polyposis, but germline (G) mutations in APC can give rise to other cancers, and somatic (S) mutations in APC can be found in multiple cancer subtypes. The clinical relevance for tumors that harbor path APC mutations is unknown. Methods: A group of patients with recurrent pancreatic cancer and their family members underwent testing (Next-generation DNA sequencing, NGS) was queried for the presence of an APC mutation. Each APC mutation identified was assessed using the NCI Clinvr data base for determination of a path/likely path APC mutation. Patient/disease characteristics and treatment (tx) information was captured from electronic medical record median. Overall survival (OS) was defined as the time of diagnosis of advanced/metastatic disease until death. Median time to progression (TTP) for each tx regimen was defined from the initiation of tx until documented disease progression. Results: A database of over 10000 patients entries from 2010 to present included 133 patients (1%) with G- or S APC mutations, of which 41 were identified as path/likely path. Of the 41 patients, 56% were male, 73% were Caucasian and 24% African Americans, with a median age of 67 (range 34-90). Only 32% of patients had known G-APC mutations, but 34% had a secondary primary, and 37% had a family history of known G-APC mutation-associated cancers. Only one patient had clinical manifestations of a polyposis syndrome. Of the 13 patients with known G-APC mutations, clinical characteristics were similar to the larger group, except that 100% of the G-APC-mutated patients were Caucasian, and the rate of family history of APC-associated cancers was 54%. Fifty-four percent of the overall group of 41 patients had a pathological diagnosis of pancreatic cancer, while the remaining 46% were amputated or duodenal cancers. (Only 2 patients %) had tail of the pancreas cancers. Of the 37 patients who had somatic tumor NGS, only 70% harbored a KRAS gene mutation. For the OS analysis (n=24), the mOS was 11.7 months (range 5.2 – 56.9). Of the 22 patients evaluable for TTP, the mTTP for SFU-based tx was 5.8 months, and 6.4 months for gemcitabine-based tx. Conclusion: APC and smoking are useful and uncommon analytes for survival rates, as well as TTP on both SFU and gemcitabine-based txs that are similar to that seen with most pancreatic adenocarcinomas. However, 30% of APC-mutated cancers are KRAS wild type, and may harbor other driving mutations. As the loss of APC function triggers an accumulation of beta-catenin, targeted therapies that inhibit beta-catenin-regulated transcription and downregulate WNT-related signaling could be a promising approach for patients whose tumors harbor path/likely path APC mutations. Research Sponsor: None.

Utility of circulating tumor DNA (ctDNA) for the detection of minimal residual disease (MRD) after curative-intent therapy for patients with localized pancreatic adenocarcinoma (PDAC): A single institution series and meta-analysis. First Author: Ujwal R. Yanala, Division of Surgical Oncology, Department of Surgery, University of Miami, Miller School of Medicine, Miami, FL.

Background: PDAC is associated with a high recurrence rate even after curative-intent surgery and perioperative chemotherapy. Detection of MRD in this setting can inform prognosis and may be actionable for innovative targeted therapies or additional chemotherapy to improve outcomes. While CA19-9 may detect disease before it is clinically apparent, it lacks specificity and up to 20% of patients (pts) are non-producers. ctDNA, while a fragile and amenable tumor biomarker, can be used to predict outcomes and inform recurrence-free survival rates, as well as TTP on both SFU and gemcitabine-based txs that are similar to that seen with most pancreatic adenocarcinomas. However, 30% of APC-mutated cancers are KRAS wild type, and may harbor other driving mutations. As the loss of APC function triggers an accumulation of beta-catenin, targeted therapies that inhibit beta-catenin-regulated transcription and downregulate WNT-related signaling could be a promising approach for patients whose tumors harbor path/likely path APC mutations. Research Sponsor: None.

Association between TP53 gain of function and loss of function mutational subgroups and survival in pancreatic adenocarcinoma. First Author: Nitzan Kott, Thomas Jefferson University, Philadelphia, PA.

Background: TP53 is a commonly mutated tumor suppressor in pancreatic adenocarcinoma (PDAC) but the clinical implications for different classes of TP53 variants remain unclear. In contrast to loss of function (LOF) mutations, TP53 gain of function (GOF) mutations alter DNA conformational binding (e.g. R175H, G245S, R249S, R228H) or modify DNA contact hotspots (e.g. R248Q, R248W, R273H) and are associated with aggressive phenotypes. Here, we analyze progression-free survival (PFS) on standard therapies and overall survival (OS) of PDAC patients (pts) within TP53 mutational subgroups: GOF, LOF, and wild type (WT). Methods: We analyzed longitudinal outcomes across 775 pts with next generation DNA sequencing (NGS) results from Perthus’s Real-World Evidence database who received at least 1 line of therapy in the advanced setting for PDAC. PFS was evaluated from initiation of 1st line for advanced disease until discontinuation. Hazard ratios and p-values were computed via Cox regression when comparing OS relative to date of advanced diagnosis and PFS on subsets who received 1st line FOLFIRINOX (FFX) or 1st line gemcitabine/nab-paclitaxel (GA). Differences in frequencies of genomic alterations between TP53 mutational subgroups were analyzed by Fisher’s exact test. Results: In the TP53 GOF subgroup, median PFS on 1st line GA was significantly worse than 1st line FFX (Table) but this difference was not observed in TP53 GOF or WT subgroups. Irrespective of 1st line therapy choice, median OS in the WT subgroup (2.1y [1.8-2.4]) was significantly longer (p<0.05) than pts with TP53 GOF (1.5y [1.3-2.3]) or TP53 LOF (1.4y [1.2-1.5]). KRAS mutations were enriched (unadjusted p<0.05) for recurrence with TP53 (97.3%) and LOF (93.3%) subgroups relative to WT (74.5%). Mutations in BRCA1/2 were less common in the TP53 GOF subgroup (2.5%) relative to LOF (5.1%) and WT (11.6%). ATM mutations as well as an expanded set of genomic alterations within the DDR pathway were also enriched with similar trends in TP53 LOF as WT. Other putative finding factors will be discussed in the context of multivariate state-of-the-art analyses. Conclusions: TP53 mutations correlated with worse prognosis in advanced PDAC. Potential predictive associations favoring FFX over GA in the TP53 LOF subgroup (but not in GOF or WT subgroups) warrant further exploration. Research Sponsor: Pancreatic Cancer Action Network; Perthus.
Characterizing the genomic landscape of locally advanced pancreatic cancer. First Author: Galileo Arturo Gonzalez Conchas, Princess Margaret Cancer Centre, Toronto, ON, Canada.

Background: Locally advanced pancreatic cancer (LAPC) accounts for approximately 30% of pancreatic ductal adenocarcinomas (PDAC). Optimal management for LAPC is controversial and com- 20
bination treatments are extrapolated from treatment guidelines for metastatic disease. The biological underpinnings of LAPC, although not equivalent to those of metastatic disease, are associated with metastatic disease. Here we characterize the genomic landscape of LAPC in a large series of prospectively sequenced PDAC.

Methods: Clinical, genomic and survival data were obtained from the COMPASS trial (NCT02758567), a prospective multi-institutional study that included patients with treatment-naive advanced PDAC, with predominantly metastatic cases due to ease of biopsy. Fresh tumor tissue was acquired by percutaneous core biopsy for real-time whole genome sequencing (WGS) and RNA sequencing (RNaseq). Laser capture micro-dissection was performed for all cases. Response to therapy was assessed every 8 weeks, and patients were followed prospectively.

Results: Of 268 patients (268 available with WGS and 253 with RNaseq), 37 (14%) had LAPC. Baseline variables were similar, with no differences between sex, age, smoking status, 24
or history of diabetes. Patients with LAPC had a lower BMI (median 22 vs 24, p=0.005) and lower baseline CA19-9 (median 488 vs 2531, p=0.002) than metastatic cases. All patients with LAPC had a low q<0.05) in addition, when measuring CD8 T cell infiltration by IHC using median cut-off values, primary site 28
biopsies had a higher CD8 T cell infiltrate compared to metastatic sites (77% vs 56% CD8-high, respectively, p<0.001).

Conclusions: These integrated genomic, RNA subtyping and early immunophenotyping of LAPC demonstrate additional potential treatment options. Further study will delineate how these genomic differences, along with better clinical features, may influence treatment decision-making and design of future clinical trials. Clinical trial information: NCT02758567. Research Sponsor: Ontario Institute for Cancer Research.

699 Poster Session
Characterization of the cachexia pathway in pancreatic ductal adenocarcinoma. First Author: Karam Ashour, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA.

Background: Cancer cachexia is characterized by progressive weight loss and skeletal muscle degradation, contributing to 35% of pancreatic ductal adenocarcinoma (PDAC) death. Cancer cachexia is present in more than 90% of patients with metastatic PDAC. Cachexia is strongly associated with metastatic disease. Here, we present comprehensive clinical and molecular characterization of the myostatin-activin pathway in PDAC.

Methods: 9,607 samples of PDAC tested at Caris Life Sciences (Phoenix, AZ) with WTS (Ulimma NovaSeq) and NextGen data sequencing (NextSeq, 922 Genes and NovaSeq, WES) were analyzed. Cachexia gene scores (GS) were calculated by averaging the post-changes of scores of activins and negative regulators, and the number of repressors in the myostatin-activin pathway. Activators were ACVR1B, ACVR1C, ACVR2A, ACVR2B, SMAD2, SMAD3, SMAD4, and TGFR2, while repressors were SMAD1, SMAD5, SMAD6, SMAD7, SMURF1, and SMURF2. The top quartile (Q4) and bottom quartile (Q1) of GS were compared using chi-squared and Fisher’s exact tests. RNA deconvolution analysis with increased expression of immune related genes (IDO1, HAVCR2, IFNG, SMAD7) were compared using chi-squared and Fisher-Exact tests. Spearman correlation linked cachexia GS with the lipid metabolizing genes (UCP3, D12, D16, D17) and ACVR2A, ACVR1B, ACVR1C, ACVR2A, ACVR2B, SMAD2, SMAD3, SMAD4, and TGFR2, while repressors were SMAD1, SMAD5, SMAD6, SMAD7, SMURF1, and SMURF2. The top quartile (Q4) and bottom quartile (Q1) of GS were compared using chi-squared and Fisher’s exact tests. RNA deconvolution analysis.

Results: Of 268 patients (268 with available WGS and 253 with RNaseq), 37 (14%) had LAPC. Baseline variables were similar, with no differences between sex, age, smoking status, or history of diabetes. Patients with LAPC had a lower BMI (median 22 vs 24, p=0.005) and lower baseline CA19-9 (median 488 vs 2531, p=0.002) than metastatic cases. All patients with LAPC had a low q<0.05) in addition, when measuring CD8 T cell infiltration by IHC using median cut-off values, primary site biopsies had a higher CD8 T cell infiltrate compared to metastatic sites (77% vs 56% CD8-high, respectively, p<0.001).

Conclusions: These integrated genomic, RNA subtyping and early immunophenotyping of LAPC demonstrate additional potential treatment options. Further study will delineate how these genomic differences, along with better clinical features, may influence treatment decision-making and design of future clinical trials. Clinical trial information: NCT02758567. Research Sponsor: Ontario Institute for Cancer Research.

700 Poster Session
Inter-reader variability of imaging biomarkers for therapeutic response in pancreatic ductal adenocarcinoma. First Author: Jon Stanley Heiselman, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Indeterminate borders of pancreatic ductal adenocarcinoma (PDAC) can impair 704
response assessment in image-based response assessment of cancer therapeutics compared to neoadjuvant chemotherapy (NAT). Previous work showed that longitudinal image registration algorithms can track treatment-related changes and produce quantitative imaging biomarkers (QIB) for TR that predict overall (OS) and recurrence-free survival (RFS). We compare inter-reader variability of these biomarkers across conventional RECIST and tumor volume QIB.

Methods: N=30 patients enrolled in a Phase II clinical trial comparing outcomes of a NAT regimen versus surgery, and baseline tumor volumes were annotated by 2 expert attending radiologists and 2 research readers. Median OS measured 12.5 months and 2.0 years since advanced diagnosis (mOS) for patients with LAPC and metastatic cases, respectively, (HR=0.95, CI=0.89-0.99, p=0.001) than metastatic cases. All patients with LAPC had a low (q<0.05) in addition, when measuring CD8 T cell infiltration by IHC using median cut-off values, primary site biopsies had a higher CD8 T cell infiltrate compared to metastatic sites (77% vs 56% CD8-high, respectively, p<0.001).

Conclusions: These integrated genomic, RNA subtyping and early immunophenotyping of LAPC demonstrate additional potential treatment options. Further study will delineate how these genomic differences, along with better clinical features, may influence treatment decision-making and design of future clinical trials. Clinical trial information: NCT02758567. Research Sponsor: Ontario Institute for Cancer Research.

Comparison of mPOF on 1-line therapies (Ga or FXX), mOS & mRFS relative to advanced diagnosis, and frequencies of co-occurring mutations (%) between patients with Wnt pathway alterations (MUT) or without (WT). (A) Comparison of mPOF on 1-line therapies (Ga or FXX), mOS & mRFS relative to advanced diagnosis, and frequencies of co-occurring mutations (%) between patients with Wnt pathway alterations (MUT) or without (WT). (B) Comparison of mPOF on 1-line therapies (Ga or FXX), mOS & mRFS relative to advanced diagnosis, and frequencies of co-occurring mutations (%) between patients with Wnt pathway alterations (MUT) or without (WT).
Conclusions: In conclusion, there is comparable mutation detection between tissue genomic DNA and blood ctDNA. The significant increase in ctDNA mutations during disease progression suggests their association with immune evasion and cancer evolution. Further studies utilizing our prospective cohort are needed to explore clinical implications of these results. Research Sponsor: None.

702 Poster Session
Clinical and prognostic characteristics of early onset metastatic pancreatic cancer. First Author: Andrea Pretta, Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy
Background: In the last decade several studies have shown an increase in the incidence of early-onset PDAC (EO-PDAC), conventionally defined as cancer that occurs in adults between the ages of 18 and 49. Clinical and prognostic data on this setting are limited and conflicting. The aim of our study was to evaluate the clinical, and prognostic differences in a large group of patients with early onset mPDAC. Methods: We retrospectively collected data from 368 patients affected with metastatic pancreatic ductal adenocarcinoma, from 3 different Italian Institutions. All patients had one or more metastatic sites, and received first-line chemotherapy. The main objective of the study was to evaluate the median overall survival in EO-PDAC patients compared to late onset PDAC (LO-PDAC), while secondary endpoint was evaluations of mPFS. Statistical analysis was performed with the MedCalc package. Results: 30 (8.1%) patients were early onset and 338 (91.9%) were late onset; median age was 46 (±5) and 68 (±8), respectively. M/F ratios were 1:1 in both group. In the overall population mOS was significantly lower in ED-PDAC patients: 10.0 versus 15.0 months (p = 0.03). Furthermore, mPFS was significantly lower in ED-PDAC patients: 5.0 versus 8.0 months (p = 0.04). ORR obtained from 244 pts were: 11% in ED-PDAC and 24.7% in LO-PDAC. Conclusions: The results of our work, although limited by the retrospective nature of the study, showed a worse prognosis for patients with early onset PDAC compared to late onsets. Further investigations will be needed to better understand this growing group of patients from a molecular and therapeutic point of view. Research Sponsor: None.

703 Poster Session
The effect of germline DNA repair mutations on radiosensitivity in pancreatic ductal adenocarcinoma. First Author: John Michael Bryant, Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
Background: The association between homologous recombination deficiency (HRD) in pancreatic ductal adenocarcinoma (PDAC) and sensitivity to platinum-based chemo-therapy has been linked to the role of germline DNA repair genes, and thus has been attributed to the efficacy of different therapies. Given the recent ALLIANCE data that chemotherapy alone is an acceptable standard of care to enhance R0 resection, the focus has shifted towards the contribution of radiotherapy. However, the relationship between germline DNA repair mutations in general and radiosensitivity remains less understood. This study explores the relationship between germline mutations and the Radio-sensitivity Index (RSI) gene signature. Methods: After obtaining institutional review board approval, a retrospective analysis was performed of patients who had both RSI and germline mutation testing (i.e., BRCA1, BRCA2, ATM, MLH1, MSH2, MSH6, PMS2, and BARD mutations) be blood DNA and tissue DNA. A single institutional review board approval, a retrospective analysis was performed of patients who had both RSI and germline mutation testing (i.e., BRCA1, BRCA2, ATM, MLH1, MSH2, MSH6, PMS2, and BARD mutations) be blood DNA and tissue DNA. A single institutional

704 Poster Session
Tumor immune microenvironment of KRAS G12C mutated pancreatic cancer as compared to other mutations and non-cancer pancreata. First Author: Vaibhav Sahai, University of Michigan, Ann Arbor, MI
Background: KRAS G12C mutation occurs in approximately 1% of pancreatic ductal adenocarcinoma (PDAC). KRAS G12C inhibitors have a reported response rate of 21-33% in patients with previously treated advanced PDAC. KRAS is a known modulator of the tumor immune microenvironment (TME) and a greater understanding of the TME in KRAS G12C as compared to other mutations is crucial for developing rational thera-peutic combination strategies in PDAC. Methods: We performed multiplex fluorescent immunohistochemistry (mIFHC) on tissue obtained from patients with historically confirmed PDA (KRAS G12C n=8; other mutations n=108) and normal pancreas (n=38). Serial staining was performed using antibodies against CD3, CD8, CD163, FoxP3 and PanCk for simple and complex phenotyping as well as spatial analyses in the TME. After tyramide based signal amplification, the slides were imaged at 20x magnification using the Mauna Quantitative Pathology workstation. Images were analyzed using inForm Cell Analysis software (Akoya Biosciences). All statistical analyses were performed using JMP Pro 13.2.0. Differences in phenotype, distances, and engagement were evaluated by 2-tailed Student’s t test or ANOVA. Results: Patients with KRAS G12C mutation had a median age of 70 (45-73) years of which majority (n=5, 62.5%) were men with advanced stage at diagnosis (n=6, 75%). The median overall survival is not yet reached (n=5, alive) after a median follow-up time of 14.4 months through reverse censoring methodology. When examining cellular infiltration, CD8+ cytotoxic T lymphocyte cells were significantly more abundant in the G12C TME compared to the cancer and non-cancer controls (p <0.01). Additionally, the relative frequency of CD4+ and Tregs (CD3+/CD8-/FoxP3+) were also significantly higher in G12C (p <0.01) while the percentage of non-functional APCs (PD1+/CD163+) of all APCs was significantly higher in G12C than cancer and non-cancer controls (p=0.03). In comparison, the PD1+ epithelial cells were much lower in G12C TME (p<0.01). The cellular engagement and interaction data from the spatial analysis in the TME will be presented at the meeting.

Conclusions: We identified increased infiltration of cytotoxic T lymphocytes and APCs in PDAC patients with KRAS G12C mutations relative to other mutations and non-cancerous pancreata. Furthermore, while all PDAs that from K-RAS mutants have minimal expression on epithelial cells suggesting a mutation specific impact and a potential role of immune checkpoint inhibitors in combination with G12C inhibitors. Research Sponsor: University of Michigan Rogel Cancer Center (TF); University of Michigan Rogel Scholar (VS).
Epidemiological characteristics of patients with pancreatic cancer with and without diabetes mellitus: A retrospective cohort study. First Author: Sarah Elizabeth Eichinger, Cook County Health, Chicago, IL
Background: Pancreatic cancer accounts for approximately 3% of all cancers diagnosed in the US and more than 8% of all cancer deaths. Despite the increasing incidence, there are few indications, mostly in patients with genetic mutations. Pancreatic cancer is associated with several risk factors including tobacco use, family history, heavy alcohol use, and diabetes mellitus (DM). In the US, more than 11% of adults have diabetes and incidence is projected to rise over the coming years. Given the risk of DM associated with pancreatic cancer, establishing preventative measures, early intervention, and appropriate management of DM is crucial to improve patient outcomes.
Methods: We used the 2016-2019 Nationwide Inpatient Sample database, the largest all-payer, inpatient care database in the US, to study patients admitted with a diagnosis of pancreatic cancer, with and without DM, to further characterize their epidemiological characteristics. Results: Characteristics of patients with and without DM and pancreatic cancer are shown in the table. There were 150,275 patients diagnosed with pancreatic cancer, of which 44,170 (29%) had a concomitant diagnosis of DM. Of patients with both pancreatic cancer and DM, 53% were women (51% in patients without DM), 64% were white (70% in patients without diabetes), and 63% had Medicare for insurance (60% in patients without DM). Conclusions: Of patients with pancreatic cancer 29% had a concomitant diagnosis of DM (p<0.00). Epidemiological characteristics of patients with pancreatic cancers with and without DM such as age, sex, and insurance status were similar between both groups. However, there was a decreased percentage of Caucasian patients with pancreatic cancer and DM compared to those without DM. Given the association of diabetes with pancreatic cancer, and rising incidence of patients with diabetes in the US, emphasis on diabetes prevention and control may be an important factor in reducing the incidence of pancreatic cancer. This study also suggests the need for further research to determine if there is an influence on survival for pancreatic cancer in patients with diabetes to decrease the burden of pancreatic cancer in the US population. Research Sponsor: None.

Predicting rapid progression and overall survival in stage II-III pancreatic cancer using a CT-based radiomic signature. First Author: Qinmei Xu, Stanford University School of Medicine, Stanford, CA
Background: We sought to assess the ability of a computed tomography (CT)-derived radiomic signature (RS) feature set to predict rapid tumor progression and overall survival (OS) in patients diagnosed with stage II-III pancreatic cancer undergoing stereotactic body radiation therapy (SBRT) in sequence with chemotherapy. Methods: We conducted a retrospective study on a cohort of patients in stage II-III pancreatic cancer patients who underwent SBRT in sequence with chemotherapy at a single institution (Stanford Hospital and Clinics). Among them, 83 had pre-SBRT contrast-enhanced CT images with segmented tumors, forming the image set, from which we extracted 9029 radiomic (quantitative pixel-level imaging characteristic) features from the segmented tumor regions-of-interest. For RS development, we divided the imaging set into a training set (n = 53) and model development and a test set (n = 30) for evaluation. We built a binary prediction model on the training set to identify patients at risk of rapid tumor progression within three months after SBRT. We utilized logistic regression with the Least Absolute Shrinkage and Selection Operator algorithm for feature selection and classification. To fine-tune parameters, we performed five-fold cross-validation on the training set, repeating each set of parameters five times. Finally, we assessed the model's performance on the test set (n = 30) using the area under the curve (AUC) value. We selected the model with the best AUC, while also generating the predictive radiomic feature set. For OS prognostication, we conducted both univariate and multivariate Cox proportional-hazards analyses using RS and clinical features (age, sex, stage, vessel involvement, tumor location, performance status, body mass index, biological equivalent dose of radiation) as potential predictors. Results: The enrolled cohort consisted of 157 men (mean age, 69 years; SD = 12) and 113 women (mean age, 69 years; SD = 13). Seventeen textural radiomic features were identified as the RS, which demonstrated a high AUC in the test set for the prediction of rapid progression (AUC 0.850, 95% CI: 0.725, 0.975). Age was associated with OS in the multivariate model while high RS (> 0.5) was independently associated with shorter OS both in univariate and multivariate models. Conclusions: CT-derived RS, combined with age, represent the most prognostic factors for stage II-III pancreatic cancer, which likely reflects underlying biology or molecular alterations, contributes to the highest HR of poor OS and provide the strongest indicator of outcome following commonly used treatments in pancreatic cancer population. Research Sponsor: None.

Contribution of neoadjuvant chemotherapy and radiation therapy (intensity-modulated radiation therapy with concurrent chemotherapy versus stereotactic body radiation therapy alone) on tumor volume regression in patients with borderline resectable or locally advanced pancreatic ductal adencarcinoma: A single institution experience. First Author: Jacob K. Jamison, Weill Cornell Medical College, New York, NY
Background: Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis with a 5-year survival rate of 3%. We examined the clinical significance of the metastatic site on survival for patients with pancreatic cancer using the Surveillance, Epidemiology, and End Results (SEER) database. Methods: We analyzed the data on mPDAC from SEER database from 2010-2020 and categorized into three groups: mPDAC with, liver-only (LO) metastasis (mets), multi-organ mets including the liver (IL), and multi-organ mets excluding the liver (EL). Patient demographics and disease characteristics were summarized using the mean for continuous variables and proportions for categorical variables. Overall survival (OS) was calculated from time of diagnosis to death or censored at a loss to follow-up. The survival curve was plotted using the Kaplan-Meier method and log-rank p-value was reported. The Cox regression model was used to study the association of site of distant metastasis on overall survival, controlling for potential confounders (age, race, treatment, etc.). Results: We identified 22642 patients with mPDAC, 15844, 4250, and 2548 with LO, IL, EL mets respectively. The mean age at diagnosis was 66 years with the majority being white (78.4%), non-Hispanic (87.1%), and from metropolitan counties (88.5%). The median OS was 4 months, 3 months, and 6 months (log-rank p < 0.001). Multivariate analysis showed a higher risk of mortality in LO (31.5%, hazards ratio (HR)=1.315, p < 0.001) and IL groups (69.2% HR=1.692, p < 0.001) than EL group (Table). Conclusions: The site of distant metastasis is an independent prognostic factor for survival in patients with mPDAC, with liver-only mets or multi-organ mets including liver having worse OS than extrapancreatic mets. Research Sponsor: None.

Contribution of neoadjuvant chemotherapy and radiation therapy (intensity-modulated radiation therapy with concurrent chemotherapy versus stereotactic body radiation therapy alone) on tumor volume regression in patients with borderline resectable or locally advanced pancreatic ductal adencarcinoma: A single institution experience. First Author: Jacob K. Jamison, Weill Cornell Medical College, New York, NY
Background: Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis with a 5-year survival rate of 3%. We examined the clinical significance of the metastatic site on survival for patients with pancreatic cancer using the Surveillance, Epidemiology, and End Results (SEER) database. Methods: We analyzed the data on mPDAC from SEER database from 2010-2020 and categorized into three groups: mPDAC with, liver-only (LO) metastasis (mets), multi-organ mets including the liver (IL), and multi-organ mets excluding the liver (EL). Patient demographics and disease characteristics were summarized using the mean for continuous variables and proportions for categorical variables. Overall survival (OS) was calculated from time of diagnosis to death or censored at a loss to follow-up. The survival curve was plotted using the Kaplan-Meier method and log-rank p-value was reported. The Cox regression model was used to study the association of site of distant metastasis on overall survival, controlling for potential confounders (age, race, treatment, etc.). Results: We identified 22642 patients with mPDAC, 15844, 4250, and 2548 with LO, IL, EL mets respectively. The mean age at diagnosis was 66 years with the majority being white (78.4%), non-Hispanic (87.1%), and from metropolitan counties (88.5%). The median OS was 4 months, 3 months, and 6 months (log-rank p < 0.001) for LO, IL, and EL groups respectively, with 2-year survival being 4.84%, 2.56% and 7.89% respectively (log-rank p < 0.001). Multivariate analysis showed a higher risk of mortality in LO (31.5%, hazards ratio (HR)=1.315, p < 0.001) and IL groups (69.2% HR=1.692, p < 0.001) than EL group (Table). Conclusions: The site of distant metastasis is an independent prognostic factor for survival in patients with mPDAC, with liver-only mets or multi-organ mets including liver having worse OS than extrapancreatic mets. Research Sponsor: None.

Impact of site of metastases in pancreatic ductal adenocarcinoma. First Author: Adel Arshad, The Ohio State University Comprehensive Cancer Center, Columbus, OH
Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has a 5-year survival rate of 3%. We examined the clinical significance of the metastatic site on survival for patients with pancreatic cancer using the Surveillance, Epidemiology, and End Results (SEER) database. Methods: We analyzed the data on mPDAC from SEER database from 2010-2020 and categorized into three groups: mPDAC with, liver-only (LO) metastasis (mets), multi-organ mets including the liver (IL), and multi-organ mets excluding the liver (EL). Patient demographics and disease characteristics were summarized using the mean for continuous variables and proportions for categorical variables. Overall survival (OS) was calculated from time of diagnosis to death or censored at a loss to follow-up. The survival curve was plotted using the Kaplan-Meier method and log-rank p-value was reported. The Cox regression model was used to study the association of site of distant metastasis on overall survival, controlling for potential confounders (age, race, treatment, etc.). Results: We identified 22642 patients with mPDAC, 15844, 4250, and 2548 with LO, IL, EL mets respectively. The mean age at diagnosis was 66 years with the majority being white (78.4%), non-Hispanic (87.1%), and from metropolitan counties (88.5%). The median OS was 4 months, 3 months, and 6 months (log-rank p < 0.001) for LO, IL, and EL groups respectively, with 2-year survival being 4.84%, 2.56% and 7.89% respectively (log-rank p < 0.001). Multivariate analysis showed a higher risk of mortality in LO (31.5%, hazards ratio (HR)=1.315, p < 0.001) and IL groups (69.2% HR=1.692, p < 0.001) than EL group (Table). Conclusions: The site of distant metastasis is an independent prognostic factor for survival in patients with mPDAC, with liver-only mets or multi-organ mets including liver having worse OS than extrapancreatic mets. Research Sponsor: None.
KRAS mutation status in the prediction of pancreatic tumor response after neoadjuvant systemic therapy and magnetic resonance-guided SBRT. First Author: Jethanandani, The University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

**Background:** Stereotactic body radiotherapy (SBRT) has been incorporated into multimodality treatment of locally advanced and borderline resectable pancreatic ductal ade- nocarcinoma (PDAC). For non-metastatic inoperable PDAC patients (pts) who receive magnetic resonance-guided SBRT (MRgSBRT), baseline features that predict for treatment response remain unsettled. In localized PDAC, multiple studies have investigated the KRAS oncogene as a prognostic factor with mixed findings. In this single institution retrospective study of PDAC pts treated with MRgSBRT, we hypothesized that KRAS mutation status would be predictive of meaningful clinical outcomes. **Methods:** From an IRB approved database, 709 pts treated with MRgSBRT between 2016 and 2022, 39 pts with non- metastatic inoperable pancreatic cancer, known KRAS mutation status, ≥ 3 months of neoadjuvant systemic therapy (NST), and at least 3 months post-R treatment follow up were extracted for analysis. Baseline demographics, tumor and treatment characteristics, and clinical endpoints including conversion to resectability, best imaging response per RECIST v1.1, pathologic response (PR) per TRG-CAP, and overall survival (OS) after MRgSBRT were collected. Objective response (ORR) on both imaging and pathology was defined as complete response (CR) + partial response (PR); disease control (DC) was defined as CR + PR + stable disease (SD). Logistic regression was used to assess correlation between baseline variables and ORR. Cox proportional hazard models were utilized to determine association with OS. **Results:** Out of 39 pts, 21 (53%) were KRAS-mutated (KRAS-mt) and 18 (47%) were KRAS wild-type (KRAS-wt). Median age was 62, 54% were male, only 1 pt had ECOG ≥ 1, and CA 19-9 at diagnosis was 197. Median duration of NST was 9 cycles, and common agents included Gemcitabine and Abraxane (21%), FOLFRINOX (28%); a combination of the two regimens (41%); or other NSTs (10%). Median MRgSBRT dose fractionation was 50 Gy (range 35 – 50) in 5 fractions; all fractions underwent adaptive optimization. Thirty pts (77%) experienced DC on imaging, 16 (43%) had ORR, and 12 (31%) were converted to resectable following MRgSBRT. Cohort median OS was 12.3 months, and pts with KRAS-mt had significantly better OS at diagnosis (18 vs 12 months, p<0.05). KRAS-mt was associated with worse ORR (p=0.04; AUC-0.73) and decreased OS (HR: 2.15; p=0.03). In a clinical model incorporating baseline characteristics (age, ECOG, radiographic staging, CA 19-9 level, and KRAS), only KRAS predicted OS (HR: 3.02 for KRAS-mt; p<0.01). KRAS-mt status was also predictive of OS among pts who underwent surgery (HR: 5.24; p=0.04). **Conclusions:** For localized PDAC pts inoperable at diagnosis who received NST followed by MRgSBRT, KRAS was the only significant predictor of ORR and OS, highlighting the need for further treatment intensification in KRAS-mt pts. Research Sponsor: None.

**TPS711**

**Trials in Progress Poster Session**

DisCoVeR: A multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial to investigate the efficacy and safety of dronabinol in the improvement of chemotherapy-induced and tumor-related symptoms in patients with locally advanced or metastatic pancreatic cancer during first-line chemotherapy. First Author: Felix Kell, Hanusch-Krankenhaus Verein für Leukämieforschung, Wein, Germany

**Background:** Patients (pts) with pancreatic cancer suffer from multiple symptoms related to the tumor itself or induced by chemotherapy (ctx). The available supportive therapy is still not able to relieve all symptoms caused by the cancer itself or by the antineoplastic therapy. Additionlly, anorexia and weight loss often result in increased metabolic fragility in this population as well as psycho-social burden and suf- fering. These are unmet needs in pancreatic cancer pts. Dronabinol has shown beneficial effects observed in cancer pts. However, evidence from randomized, placebo controlled trials in the use of cannabinoids for the treatment of cancer related anorexia-cachexia syndrome are lacking. Aim of this phase II trial is to investigate the efficacy and safety of dronabinol (orally administered tetrahydrocannabinol (THC)) as an adjuvant, individually titrated therapy to first-line standard chemotherapy in pts with metastatic pancreatic cancer for improvement of ctx- and tumor-related symptoms. **Methods:** Locally advanced or metastatic pancreatic cancer pts from Austria and Germany with an age of ≥ 18 yrs tolerating FOLFRINOX or gemcitabine/ nab-paclitaxel based ctx are eligible for enrollment. **Exclusion criteria:** Use of dronabinol, cannabis-based medicine with THC or marinhuana or relevant psychiatric disorders. The study duration for each patient will be a maximum of 18 weeks treatment. Eligible pts are randomized 1:1 for treatment with dronabinol oral solution (2.5%) or placebo oral solution stratified by underlying ctx. The primary endpoint variable is the standardized area under the curve of the EORTC QLQ-C30 symptom summary score on the on-treatment period. Secondary endpoints include: other quality of life parameters, changes in Gonzalez Prognostic Score, mean time to critical weight-loss (5%), ctx dose intensity over the treatment of 18 wks, adverse events/reactions, PFS and OS. Changes from baseline for bioelectrical impedance analysis parameters (eg. fat- free mass, total body water, fat mass and phase angle) and hand grip strength will be evaluated. Estimating a difference of 20% in the primary endpoint between the treatment groups with a power of 80% and an expected standard deviation of 0.3 a total sample size of 74 assuming a balanced design is required. A total sample size of 104 pts is needed with expected drop-out rate of 30 pts. Enrollment started in 2019 and continues until 2024. The first phase is the dose escalation phase, the second phase is the dose-escalation phase, the third phase investigates the impact of individually dosed dronabinol in cancer pts (Registration: NCT03984214). Clinical trial information: NCT03984214. Research Sponsor: AGMT.

**TPS710**

**Trials in Progress Poster Session**

Epidemiological characteristics of gastric and pancreatic cancers in Latin America: The LACOG 0222 GASPAR study. First Author: Renata D’Alpino Peixoto, Hospital das Clínicas, São Paulo, Brazil

**Background:** Gastric and pancreatic tumors remain among the cancers with the poorest prognoses in both high and low/middle-income countries. Data on the clinicopatho- logical characteristics, standard treatments, and outcomes of these tumors are scarce in Latin America. This study is the first comprehensive effort to report epidemiological and clinical data in this region. **Methods:** The LACOG 0222 GASPAR trial (NCT05924789) is a retrospective and prospective (bidirectional) observational cohort study. Enrollment of 200 patients across 15 sites in Latin America is planned. 120 patients in cohort A (gastric cancer) and 80 patients in cohort B (pancreatic cancer). No interventions are proposed. Eligibility criteria include age ≥ 18 years, histological diagnosis of gastric and gas- troesophageal junction cancer (cohort A) or A pancreatic cancer (cohort B), advanced disease diagnosis since January 2019, and availability of adequate medical data for data collection. The primary objective is to describe the clinical characteristics, treatment patterns, and outcomes of patients with gastric and pancreatic cancer in Latin America. Data on patients’ clinical characteristics, demographics, tumor pathological features, surgical therapy, radiotherapy, chemotherapy, and target therapy will be collected. Patient outcomes, such as recurrence-free survival, progression-free survival, and overall survival will also be collected. Patients will be followed up for up to 3 years after diagnosis. No a priori sample-size calculations were performed. The demographic and underlying disease characteristics will be evaluated using descriptive statistics. Time- to-event outcomes (death-free survival, progression-free survival, and overall survival) will be estimated using the Kaplan-Meier method. From August 2023 to September 2023, 240 patients will be enrolled. The target enrolment is expected to be completed by February 2024. The results are expected to be presented in August 2024. Research Sponsor: Astellas.

**TPS712**

**Trials in Progress Poster Session**

A phase 1b/2 trial of pepinemab and avelumab as second line therapy for patients with metastatic pancreatic adenocarcinoma. First Author: Bailey Hilty, University of Rochester Cancer Center & Wilmot Cancer Institute, Rochester, NY

**Background:** Pancreatic adenocarcinoma (PDAC) is a leading cause of cancer-related mortality with poor prognosis despite maximal therapy and is unresponsive to immune checkpoint blockade (ICB) therapy. To address this, we hypothesized that the inclusion of an antibody (Avelumab) that targets the Cell Surface Antigen (801) in combination with an anti-PD-L1 (pembrolizumab) with anti-PD-L1 (avelumab) in patients with chemotherapy-refractory PDAC. Patients must have failed first-line 5-fluorouracil or gemcitabine-based combination chemotherapy. The study follows a dose de-escalation schema starting at a dose combination of 20mg/kg pembrolizumab and 800mg avelumab every two weeks. Patient accrual for phase 1b utilizes the Bayesian Optimal Interval Design (BDON) targeting a dose-limiting toxicity rate of 30% or less. After 16 subjects receive a given combination dose, a Simon’s two stage assessment of futility will be undertaken with expansion to phase 2 if 2 or more subjects demonstrate response. The trial is designed to evaluate a total cohort of 40 subjects and powered to detect a response rate of 23% or greater, with alpha set at 0.1% and 80% power. Treatment response will be assessed via RECIST v1.1 criteria with surveillance CT prior to enrollment and after completion of two cycles (8 weeks). Baseline and on-treatment tumor biopsies (after completion of one cycle, 4 weeks) are performed to analyze changes in immune, stromal, and genomic profiles to elucidate mechanisms of treatment response and failure. Patient reported outcomes are incorporated (FACT-Hep and FAACT subdomains) to assess disease-specific symptoms. To date, 7 patients have been enrolled (Clinical Trial NCT05102721). Clinical trial information: NCT05102721. Research Sponsor: Gateway for Cancer Research, Conquer Cancer Foundation ASCO; Vaccinex.
A phase 1 trial of combined MEK, STAT3 and PD-1 inhibition in metastatic pancreatic ductal adenocarcinoma (PDAC). First Author: Peter Joel Rosein, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: PDAC is characterized by its innate and acquired resistance to both MAPK pathway inhibition and immune checkpoint (e.g. PD-1/PD-L1) inhibition (ICI) via multiple mechanisms. In preclinical models of PDAC, combined MEK and STAT3 inhibition (MEKi+STAT3i) unovers stromal plasticity by attenuating cancer-associated fibroblasts (CAF) with IL-6/CXCL1-secretory phenotypes while enriching for Ly6a/CD34-expressing CAF phenotypes with mesenchymal stem cell-like features. This remodeling of CAF heterogeneity is-at least in a striking attenuation in and reprogramming of tumor-associated macrophages (TAMs) as well as enhanced trafficking of CDb T cells, which exhibit a distinct effector and anti-apoptotic transcriptional program. The addition of MEK+STAT3i to PD-1 blockade overcomes ICI resistance by significantly enhancing the recruitment, degranulating capacity, and functional cytotoxicity of CDb T cells, thereby augmenting antitumor immune responses and improving survival in the tumor. Furthermore, a patient with refractory PDAC treated off-label with this combination achieved a meaningful response. Based on this strong rationale, a phase 1 trial was initiated to test the combination of MEK+STAT3 and PD1 inhibition in patients with metastatic PDAC. Methods: NCT05440092 is an open-label, prospective, single-institution phase 1 trial testing the safety, preliminary efficacy, and biomarkers of response to the combination of trametinib (MEKi), ruxolitinib (JAK2/STAT3 inhibitor) and retifanlimab (PD-1 inhibitor) in patients with metastatic PDAC. Patients with metastatic PDAC who have had disease progression on at least one line of prior therapy, with good organ function, preserved performance status and, without major intercurrent illness are eligible. Patients must have an accessible lesion for biopsy and must be willing to undergo this research biopsy at baseline and on treatment. Part 1 of the study is a dose-escalation phase with 3 dose levels and a target dose of trametinib 2mg orally daily, ruxolitinib 15mg orally twice daily, and retifanlimab 500mg intravenously every 28 days. All patients are being dosed using the novel Bayesian keyhole. 1-9 patients will be treated to get to the potential maximum tolerated dose (MTD). Dose level 1 has been completed without any dose-limiting toxicities seen. Part 2 is an expansion phase which will accrue an additional 20 patients. All patients in part 1 and 2 will have core-needle biopsies pre-treatment and after 4 weeks. Serial blood samples will be collected for immune profiling at baseline and at day 1 of week 2 of study treatment. Part 1 will comprise a six-patient safety run-in with a dose-de-escalation design in which patients will be treated according to Arm C with a plan for subsequent enrollment of 14 additional patients per arm (N=42) in Part II. The primary endpoint is CD8+ T-cell infiltration at the time of surgery compared between combination groups. Tumor biopsies will be obtained at baseline and after 4 weeks. Analysis of dose level 2 will be performed with a maximum of 12 patients at dose level 2. The tumor biopsies will be obtained at baseline and after 4 weeks. Analysis of dose level 3 will be performed with a maximum of 12 patients at dose level 3. The combined use of a VEGF receptor tyrosine kinase inhibitor (TKI) and checkpoint inhibitor is already standard in care above dose level 3. This study will evaluate the safety, preliminary efficacy, and biomarkers of response to the combination of trametinib, ruxolitinib and retifanlimab in patients with metastatic PDAC. First Author: Brian Hemendra Ramnaraign, University of Florida/UF Health Cancer Center, Gainesville, FL

Background: Checkpoint inhibitor therapy represents a significant advance in cancer care however it is not an effective intervention in the treatment of several immunologically cold cancers. Some ductal malignancies, including PDAC, show no significant response to checkpoint inhibitors have produced objective response rates ranging from 0-6%. VEGF is thought to play a key role in modulating the anti-tumor immune response as it is secreted by tumors and leads to endothelial cell proliferation, vascular permeability, and vasodilation. This in turn leads to the development of an abnormal vasculature with excessive permeability, often score of the reason for poor outcome of patients with PDAC. VEGF inhibits dendritic cell differentiation, limiting the presentation of tumor antigens to CD4 and CD8 T cells. Through the inhibition of VEGF, it may be possible to potentiate the effect of immune checkpoint blockade. Combined use of a VEGF receptor tyrosine kinase inhibitor (TKI) and checkpoint inhibitor is already standard in care above dose level 3. COVALENT: A phase 1/1b dose finding study of BMF-219, an oral covalent menin inhibitor, in adults with locally advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC), pancreatic cancer (PDAC) and colorectal cancer (CRC) with activating KRAS mutations. First Author: Peter Joel Rosein, University of Miami Sylvester Comprehensive Cancer Center, New York, NY

Background: BMF-219 is a selective covalent inhibitor of menin, a transcriptional regulator of oncogenic signaling pathways in multiple cancers, that inhibits the menin/ MYC interaction and downregulates the expression of MYC and MYC target genes, including KRAS. In addition, inhibition of the menin complex by BMF-219 alters function of the AP-1 transcription factor, JunD, a crucial factor for KRAS-driven tumorigenesis. Further, inhibition of the menin-MLL complex suppresses expression of Rasgrf1, a parameter immune profiling using mass cytometry and bulk RNA sequencing; blood is be collected at baseline and on treatment. Biopsies are being analyzed by multipa-
A phase II telemedicine study of pemigatinib in adult patients with unresectable or metastatic pancreas cancer with FGFR2 gene fusions or other FGFR2 genetic alterations. First Author: Zachary Rischo, The Ohio State University, Columbus, OH

Background: Advanced pancreas cancer has a poor prognosis with few effective targeted therapies. Given this current state, novel therapies for pancreas cancer are an unmet need. Genomic alterations in FGFR, including fusions and point mutations are known driver mutations in cancer. FGFR kinase inhibitors have been FDA approved in cholangiocarcinoma and urothelial carcinoma, however, have not been well studied in other cancers. Our team previously identified and treated four patients with advanced pancreas cancer and FGFR2 fusions with FGFR kinase inhibitors resulting in durable responses and prolonged survival. Additionally, through a review of Foundation Medicine’s clinical genomic database, consisting of 30,229 pancreas cancer tumors, we determined that FGFR2 fusions have a prevalence of approximately 1% in pancreas cancer (0.8%). Our observations provided evidence that FGFR targeted therapy results in excellent clinical outcomes. We hypothesize that FGFR altered pancreas cancer treated with a FGFR kinase inhibitor will result in durable responses. We developed a phase 2, telemedicine trial of pemigatinib, an FDA approved FGFR kinase inhibitor, in FGFR2 altered pancreas cancer. Since the COVID-19 pandemic, telemedicine is used in routine oncology care and clinical trials and is associated with cost savings for patients. The growing adoption of this technology provides an opportunity to enhance the study of ultra-rare cancers. Methods: The trial consists of unselectable or metastatic pancreas cancer of any histology in two cohorts: 1) Primary cohort of FGFR2 fusions (n=30) and 2) exploratory cohort of other known activating mutations in FGFR (n=10). Patients are identified from across the United States through Foundation Medicine, Caris Life Sciences, and the Pancreatic Cancer Action Network. Eligible patients will be treated with oral pemigatinib through telemedicine by investigators at The Ohio State University in collaboration with local oncologists for supported treatment. Of this trial up to 30 eligible patients are planned. Patients will be treated for 3 cycles based on an expected overall response rate of $\geq 33\%$ and $<10\%$ as unfavorable response, at one-sided Type I error of 0.05, 90% power and up to 13% attrition rate. Results: The primary objective is overall response rate. Secondary objectives are overall survival, progression free survival, and duration of response. Exploratory objectives are associations of circulating tumor DNA with response to treatment. Additional, telemedicine is a novel tool that can aid in the study of ultra-rare cancers and reduce barriers to patient participation in clinical trials. Research Sponsor: Incyte Corporation.

A phase II open-label study of enfurambot vedotin in patients with previously treated locally advanced, recurrent, or metastatic pancreatic adenocarcinoma (EPIC). First Author: Anup Kasi, University of Kansas Cancer Center, Kansas City, KS

Background: Nectin-4 is a type I transmembrane protein member of the nectin family involved in the maintenance of adhesions junctions. In contrast to its limited expression in normal tissues, aberrant overexpression of nectin-4 has been identified in various solid tumors, including in pancreatic adenocarcinoma. About 71% of human PDAC specimens stain positive and 13% stain strongly positive for nectin-4. Mechanistically, nectin-4 has been associated with various pro-oncogenic cellular processes, including the promotion of tumor cell proliferation and migration and microenvironmental activation. It interacts with ERBB2/HER2 and activates Rac1 (small G protein) to ultimately upregulate PI3K-AKT pathway signaling, leading to cell survival and proliferation. Enfurambot vedotin (EV) is an antibody-drug conjugate that delivers the microtubule-disrupting agent monomethyl auristatin E (MMAE) to cells expressing Nectin-4. EV is FDA approved as a single agent for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy based on the EV-301 Trial which demonstrated overall survival benefit. Taken together, the above data and the efficacy seen in bladder cancer were the reasons for evaluation of EV in advanced pancreatic adenocarcinoma. Methods: Design: Open-label, phase II single-arm trial of EV (n=28) in previously treated locally advanced, recurrent, or metastatic pancreatic adenocarcinoma. Treatment schedule: EV 1.25 mg/kg administered IV on D1, D8, D15 every 28 days until disease progression or unacceptable toxicity. Imaging assessment will be done every 8 weeks. A biopsy prior to therapy and a biopsy on treatment (between days 15-21 of cycle 1) is required. Eligibility: Patients with previously treated, locally advanced, recurrent, or metastatic pancreatic adenocarcinoma. Inclusion criteria also include EGOC PS 0-1 and at least 1 line of prior therapy. Objectives: The primary objective is to determine anti-tumor activity by overall response rate using RECIST v1.1. Secondary objectives include safety, duration of response, disease control rate, progression-free survival and overall survival. Exploratory objectives include Nectin-4 expression (H-score) in tumor tissue and the relationship between the mutational profile of the tumor and response. Statistical Plan: A Simon’s two-stage Minimax design will be used. In the first stage, 10 pts will be accrued. If there is less than 1 response in the first 10 pts, the study will be stopped for futility. Otherwise, 10 additional pts will be accrued for a total of 28 pts. The null hypothesis will be rejected if 3 or more responses are observed in 28 pts. Enrollment is currently ongoing. Clinical trial information: NCT05915351. Research Sponsor: Astellas Pharma Global Development, Inc./Seagen Inc.

PANOV-4 (EF-39): Pilot study of tumor treating fields (TTFields) therapy with atezolizumab, gemcitabine (GEM), and nab-paclitaxel (NabP) as first-line treatment for metastatic pancreatic adenocarcinoma (mPDAC). First Author: Thomas Steuerfel, Universitätsklinikum Uln, Ulm, Germany

Background: TTFields are electric fields that exert physical forces to disrupt cellular processes critical for cancer cell viability and tumor progression. TTFields therapy has non-invasive, locoregional, and is delivered via a portable electric field generator and skin-placed arrays. TTFields therapy has low risk of systemic toxicity and is approved for glioblastoma (and grade 4 glioma in Europe), and pleural mesothelioma. In vitro, addition of TTFields (150 kHz) application decreased pancreatic cancer cell proliferation and clonogenicity; in vivo, TTFields concomitant with chemotherapy (chemo) had greater antitumor effect than chemo alone in orthotopic pancreatic tumors. Co-application of TTFields with immune checkpoint inhibitors (ICIs) significantly decreased tumor volume, increased tumor infiltration and IFN-y production, and did not impede ICI-induced effector memory T-cell production versus in vivo controls. The pilot (phase 2) PANOV-4 clinical study (NCT01971281) showed safety and feasibility with TTFields therapy plus NabP and GEM in metastatic and locally advanced pancreatic adenocarcinom (LAPC). The randomized, pivotal (phase 3) PANOV-3 clinical study (NCT03374791), evaluating TTFields therapy with GEM and NabP in LAPC, is ongoing. Methods: PANOV-4 (pilot, single-arm clinical study) assesses the safety and efficacy of TTFields therapy (NovoTTF-200T device) concomitant with atezolizumab, GEM, and NabP as 1L treatment for mPDAC. Eligible patients (pts) are $\geq 18$ years of age and have a new mPDAC diagnosis, measurable abdominal disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, and no prior systemic PDAC therapy. Atezolizumab (1680 mg, IV infusion) is given before chemo on day 1 of each 28-day cycle, with NabP (125 mg/m$^2$ IV) and GEM (1000 mg/m$^2$ IV) given on days 1, 8, and 15. TTFields therapy (150 kHz) is delivered for $\geq 18$ h until disease progression per RECIST v1.1 or loss of clinical benefit. Following an accrual period of 4 weeks (wk), patients are randomized 1:1:1:1 to either 1) supportive care only (SC) to hasten on-site visit. The primary endpoint is disease control rate (DCR). Secondary endpoints include overall survival (OS), progression-free survival (PFS), 1-year OS rate, objective response rate, PFS at 6 mo, duration of response, and safety. Pts are required to achieve 80% power (1-sided alpha 0.05) to detect a 63% DCR vs historical 48% DCR in pts with mPDAC receiving 1L GEM and NabP. Clinical trial information: EUCTR2022-003157-55. Research Sponsor: Novocure, Inc.

Background: With very low survival rates, pancreatic cancer (PC) remains a disease in need of diagnostic and therapeutic innovation and novel biomarkers to guide and optimize treatment decisions are urgently needed. Analysis of circulating tumor DNA (ctDNA) has been shown to be a highly accurate method for determining treatment efficacy and detecting molecular residual disease (MRD) in patients (pts) with various cancer types as compared to tumor markers and imaging modalities. However, it has been reported that the ctDNA detection rate in PC using existing tumor-agnostic ctDNA assays was lower than those in other cancer types because of the high stromal and low cellular features of PC, which prevents the shedding of ctDNA into blood circulation. Even in advanced cancers, the sensitivity of ctDNA utilizing tumor-agnostic mutation panels is much lower as compared to that in tumor tissue specimens. The Invitae Personalized Cancer Monitoring test is a novel and highly sensitive, tumor-informed MRD detection assay. MRD assessment as well as recurrence and treatment response monitoring using this novel assay could lead to the development of improved treatment algorithms for pts with PC. The ARTEMIS-PC study (UMIN000043561) aims to evaluate the clinical utility of the Invitae Personalized Cancer Monitoring test in pts with resectable and unresectable PC.

Methods: This is a multi-site, prospective, observational trial in Japan of 150 pts with resectable (50) and unresectable (100) PC. The main eligibility criteria are histopathologically diagnosed as adenocarcinoma, no prior treatment for PC, scheduled to undergo surgery for resectable PC or receive systemic therapy for unresectable PC. In resectable PC cohort, blood samples will be collected before surgery and at 1, 3, 6, 9, 12, 18, and 24 months after surgery, and imaging study will be performed before surgery, and at 3, 6, 9, 12, 18, and 24 months after surgery. In the unresectable PC cohort, blood samples will be collected before treatment and at 4, 8, 12, 16, 24, 32, 40, and 48 weeks on treatment, and imaging study will be performed before treatment and every 8 weeks on treatment until 48 weeks. Primary endpoint in the resectable PC cohort is success rate of creating personalized panel using tumor tissue obtained by EUS-FNA/FNB, and that in unresectable PC cohort is rate of concordance of KRAS mutations between tumor tissue and blood samples. Key secondary endpoints in resectable PC cohort are rate of ctDNA positivity for each cancer stage before neoadjuvant chemotherapy and 4 weeks after surgery, and that in unresectable PC cohort is pretreatment ctDNA detection rate for each disease stage. Active enrollment started in December, 2022 and 21 pts with resectable PC and 64 pts with unresectable have been enrolled as of September 2023. Clinical trial information: NCT06043921. Research Sponsor: Invitae.

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Oral Abstract Session

Adjuvant radiotherapy after curative resection of hepatocellular carcinoma with narrow margin (≤1 cm): A phase 2, multicenter, randomized controlled trial.

First Author: Kuang Ming, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: RAISE is a multicenter, randomized, open-label, parallel-group phase 2 trial, aiming to assess the efficacy and safety of intensity modulated radiation therapy (IMRT) compared with active surveillance in hepatocellular carcinoma (HCC) patients with narrow margin (≤ 1 cm) following curative resection. Methods: HCC patients with narrow margin were randomly assigned in a 1:1 ratio to receive either IMRT (Surgery-IMRT group) or active surveillance (Surgery group) after hepatectomy. Randomized stratification factors include tumor size (< 5 vs. > 5 cm) and microvascular invasion (presence vs. absence). In the Surgery-IMRT group, patients received IMRT within 1-3 months after surgical resection. The prescription dose was planned at 50-60 gray in 29-30 fractions over 5-6 weeks. The primary endpoint was recurrence free survival (RFS). The secondary endpoints were safety and overall survival (OS). The planned sample size was 148 patients in total to obtain an improvement in the 2-year RFS rate from 45% to 65%, to detect a hazard ratio (HR) of 0.54, with a one-sided alpha of 5% and 80% power. Results: Between January 15, 2015, and September 15, 2023, 148 patients from 6 hospitals in China were randomized: 74 patients were allocated to the Surgery-IMRT group and 74 to the Surgery group. The median follow-up duration was 27.4 months (95% confidence interval [CI] 23.2-29.2 months). The 2-year RFS was 78.37% (95% CI 64.35%-87.40%) for the Surgery-IMRT group and 57.43% (95% CI 43.25%-69.28%) for the Surgery group (P=0.028). The median OS was not reached for the two groups. The following radiotherapy-related grade 3-4 adverse events were seen: 3 thrombocytopenia, 3 neutropenia, and 1 hemoglobin decreased. Conclusions: In conclusion, this trial showed that the adjuvant IMRT following curative resection can bring survival benefits of RFS for HCC patients with narrow margin. Clinical trial information: NCT03732105. Research Sponsor: None.

723
Poster Session

Income and its impact on adenomatous neoplasms outcomes: An analysis of the National Cancer Database.

First Author: Eric G. Nielsen, Creighton University School of Medicine, Omaha, NE

Background: Adenomatous neoplasms of the small intestine are rare benign tumors but are occurring with increasing incidence. They exhibit a slight male predominance, with a median age of diagnosis in the 6th decade of life. The duodenum is the most frequent location of onset. Proposed environmental risk factors include high animal fat and protein diets, intestinal flora composition, and hereditary factors. Additionally, intestinal diseases, such as Crohn’s disease or Lynch syndrome, predispose individuals to develop small intestine adenomatous neoplasms. Despite this knowledge, the National Cancer Database (NCDB) research exists analyzing the association between survivability and income. Therefore, the objective of this study is to investigate overall survival rates among individuals with adenomatous neoplasms based on income levels. Methods: The NCDB was used to identify patients diagnosed with small intestine adenomatous neoplasms from 2004 to 2019 using the histology code 8140 as assigned by the Commission on Cancer Accreditation program. Kaplan-Meier, ANOVA Chi-square tests were performed, and data were analyzed using SPSS version 27. Statistical significance was set at α = 0.05. Results: Of 19,582 patients included in the sample, 6,326 (30.8%) were from the highest income bracket, defined as annual income greater than $46,000, while 3,629 (24.4%) were from low-income brackets, defined as earnings less than $30,000. High-income patients experienced longer mean overall survival (58.5 months) compared to middle (49.7 months) and low (46.7 months) income patients (p<0.001). After controlling for age at diagnosis, sex, race, facility type, surgery status, adjunctive therapies, and insurance type, both the low- and middle-income brackets were associated with an independent increase in hazard (HR = 1.284 and 1.177 respectively; p<0.001). High income was associated with fewer comorbidities (72.2%) compared to low (65.9%) and middle-income (68.4%) patients (p<0.001). High-income patients were more likely to be treated at academic facilities (41.9%) compared to low (39.2%) or middle-income (35.4%) individuals (p<0.001), which have longer survivability (58.9 months vs. 47.8 months in non-academic facilities; p<0.001). Additionally, high income was also associated with increased rates of private insurance ownership (38.0%) while low-income individuals were more likely to have Medicaid (5.5%) or be uninsured (5.1%; p<0.001). No significant differences were found in tumor grade or differentiation, staging, histological diagnosis, or surgery type. This study indicates an association between high-income patients and increased survivability, while also observing an association with low-income and decreased survivability. Further research is required to assess specific environmental risk factors of adenomatous neoplasms and their relation to income level. Research Sponsor: None.

724
Poster Session


First Author: Lauren E. Schleimer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Small bowel adenocarcinoma (SBA) is a rare malignancy with poor prognosis. Data describing the clinical and pathologic characteristics of this disease are sparse, and few studies examine the genetic footprint of SBAs within the continuum of the gastrointestinal tract.

Methods: All patients with small bowel adenocarcinoma for whom primary tumor tissue was available from 1993 to 2021 at six institutions were included. A hidden genome classifier (HGC) was developed based on genomic features from 286 gastroesophageal cancers (foregut) and 286 colorectal cancers (hindgut) using targeted tumor sequencing. The SBAs were run through the HGC to obtain the predicted probability of either foregut or hindgut lineage. For patients submitted to curative intent resection, overall survival (OS) was calculated from 90 days post resection until date of last follow up. Cox regression was used to examine factors associated with narrow margin (≤1 cm): A phase 2, multicenter, randomized controlled trial. Adjuvant radiotherapy after curative resection of hepatocellular carcinoma with narrow margin (≤1 cm): A phase 2, multicenter, randomized controlled trial. Age at Diagnosis (years) Lymph Node Positive Multivariable Cox regression model for overall survival in patient with small bowel adenocarcinoma. Hazard Ratio (95% CI) p-value

Characteristic | Hazard Ratio (95% CI) | p-value
--- | --- | ---
Prediction Group | | |
Mixed-Type | – | –
Foregut | 1.87 (0.97 – 3.60) | 0.064
Hindgut | 1.7 (1.54 – 1.97) | 0.001
Age at Diagnosis (years) | | |
Lymph Node Positive | | |
Lymphovascular Invasión Positive | | |

Multivariable Cox regression model for overall survival in patient with small bowel adenocarcinoma.

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**Table 1.**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Hispanic</th>
<th>Non-Hispanic White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>11.5 (11.3-11.6)</td>
<td>6 (5.4-6.3)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>13 (12.1-13.5)</td>
<td>12 (12.2-12.6)</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>36 (35.8-36.3)</td>
<td>44 (43.8-44)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>2.2 (2-2.3)</td>
<td>0.9 (0.9-1.0)</td>
</tr>
<tr>
<td>Anus, Anal Canal and Aneumrectum</td>
<td>1.2 (1.2-1.3)</td>
<td>2.1 (2.0-2.1)</td>
</tr>
<tr>
<td>Stomach</td>
<td>10.9 (10.8-11)</td>
<td>5.7 (5.7-5.8)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>2.8 (2.7-2.9)</td>
<td>1.8 (1.7-1.9)</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>1.6 (1.6-1.7)</td>
<td>2.2 (2.2-2.2)</td>
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</table>

**Gastrointestinal cancer trends in the Hispanic population:**

**A SEER database population study (2000–2019).** First Author: Sharon Hechtler, Hackensack Meridian University Medical Center, Brick, NJ

**Background:** Cancer continues to be the leading cause of death in the Hispanic population. Gastrointestinal cancer surveillance data in Hispanic individuals has only recently become available in the last 3 decades. Differences in incidence rates among Hispanics and Non-Hispanic Whites (NHWs) need further elucidation. In this study, we analyzed trends in Hispanics and NHW populations across multiple gastrointestinal cancers. Methods: Gastrointestinal cancer (liver, colon and rectum, pancreas, esophagus, gallbladder, stomach, small intestine, anus, anal canal and anorectum) diagnosed between 2000-2019 were identified in the Surveillance, Epidemiology, and End Results Program (SEER) Database. We calculated incidence rates, confidence intervals and incidence rate ratios. Rates are age-adjusted and are adjusted to the 2000 US standard population. Rate ratios are the rounded rates in Hispanic individuals divided by the rounded rates in NHWs. Results: There was a higher incidence of liver, gallbladder, and stomach cancers among Hispanics when compared to NHWs between the years 2000-2019. Liver cancer incidence rate (11.5 per 100,000) in Hispanics compared with (6.3 per 100,000) in NHWs with an incidence rate ratio of 1.9. Lower incidence rate ratio was seen for anus, anal canal and anorectum cancers in Hispanics compared to NHWs. The incidence rate is (1.2 per 100,000) in Hispanics compared with (2.1 per 100,000) in NHWs with an incidence rate ratio of 0.6. Remaining cancers had incidence rate ratios less than 1.0 and were more likely to occur in NHWs. Conclusions: This study illustrates differing incidence rates of multiple gastrointestinal cancers among Hispanics compared to NHWs. Liver, gallbladder and stomach cancer incidence rates in Hispanics is double that of NHWs. Interestingly, the remaining gastrointestinal cancers had higher incidence rates among NHWs. Further research is warranted to understand the differences in incidence observed in an urban setting and 15% (10%) of NHWs had Medicaid or no insurance. Minority participants were younger on average than non-minority participants (median 58.7 vs 63.1, p<0.001), more likely to live in urban settings (92.7% vs. 82.9%, p<0.001) and have Medicaid or no insurance (26.5% vs. 6.1%, p<0.001). Over one-third (37.9%) of Hispanic, 23.0% of Asian, and 13.3% of Native American participants were NHW, while 13.0% had Medicaid or no insurance. Women’s participation varied across the cancer type, ranging from 8.3% for esophageal to 56.2% for biliary tract, as did minority participation, ranging from 5.6% for esophageal to 36.6% for gastric/GJE. Conclusions: Our findings suggest that racial/ethnic minorities, the elderly, and those residing in non-urban settings were less likely to enroll in SWOG SWOG gastrointestinal cancers trials than were whites, younger patients, and urban residents. Efforts are needed to enhance diverse enrollment, to break down barriers preventing minority participation, and to improve trial access to minimize disparities. Research Sponsor: NIH/NCI grants U10CA180888 and U10CA180819.

**Results:**

- **Trends:** There was a higher incidence of liver, gallbladder, and stomach cancers among Hispanics when compared to NHWs between the years 2000-2019. Liver cancer incidence rate (11.5 per 100,000) in Hispanics compared with (6.3 per 100,000) in NHWs with an incidence rate ratio of 1.9. Lower incidence rate ratio was seen for anus, anal canal and anorectum cancers in Hispanics compared to NHWs. The incidence rate is (1.2 per 100,000) in Hispanics compared with (2.1 per 100,000) in NHWs with an incidence rate ratio of 0.6. Remaining cancers had incidence rate ratios less than 1.0 and were more likely to occur in NHWs. Conclusions: This study illustrates differing incidence rates of multiple gastrointestinal cancers among Hispanics compared to NHWs. Liver, gallbladder and stomach cancer incidence rates in Hispanics is double that of NHWs. Interestingly, the remaining gastrointestinal cancers had higher incidence rates among NHWs. Further research is warranted to understand the differences in incidence observed in an urban setting and 15% (10%) of NHWs had Medicaid or no insurance. Minority participants were younger on average than non-minority participants (median 58.7 vs 63.1, p<0.001), more likely to live in urban settings (92.7% vs. 82.9%, p<0.001) and have Medicaid or no insurance (26.5% vs. 6.1%, p<0.001). Over one-third (37.9%) of Hispanic, 23.0% of Asian, and 13.3% of Native American participants were NHW, while 13.0% had Medicaid or no insurance. Women’s participation varied across the cancer type, ranging from 8.3% for esophageal to 56.2% for biliary tract, as did minority participation, ranging from 5.6% for esophageal to 36.6% for gastric/GJE. Conclusions: Our findings suggest that racial/ethnic minorities, the elderly, and those residing in non-urban settings were less likely to enroll in SWOG SWOG gastrointestinal cancers trials than were whites, younger patients, and urban residents. Efforts are needed to enhance diverse enrollment, to break down barriers preventing minority participation, and to improve trial access to minimize disparities. Research Sponsor: NIH/NCI grants U10CA180888 and U10CA180819.

**Utility of gene expression-based cancer classification in diagnosis of malignant peritoneal mesothelioma (MPMe): Filling in the gaps in standard pathologic work-up for a rare cancer.** First Author: Joelle Allam, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Malignant peritoneal mesothelioma (MPMe) is a rare cancer (incidence of 0.12 new cases per 100,000 and a posteriori diagnostic challenge), requiring skillful evaluation by expert pathologists. Subjective and experiential immunophenotyping coupled with inattention to this rare entity causes delayed or misdiagnosis and leads to suboptimal treatment and outcomes. Gene-expression-based cancer classification offers an objective molecular assessment of the value of tumors for cancers with uncertain diagnosis varying across diagnostic accuracy for MPMe compared to standard pathology. Methods: We retrospectively evaluated 23 patients (pts) with cancer of unknown primary (CUP) or uncertain diagnoses, with peritoneal/retroperitoneal carcinomatosis and reported as malignant mesothelioma using a 92-gene assay (CancerTYPE ID), a validated classifier for predicting tumor types, between January 2013 to December 2016. Pathology was verified by central review. Clinicopathologic data including immunohistochemistry (IHC) was collected using archived pathology specimens and reports. Results: Pts had a median age of 64 years (range: 39 – 93) at diagnosis, 57% were females and 85% had biopsy from omentum/peritoneum. Original histopathology was reported as poorly differentiated in 81% and as adenocarcinoma, carcinoma and malignant neoplasm in 10 (43%), 7 (30%) and 6 (27%) of cases, respectively. The number of IHC stains performed ranged from 0 and 28 (median: 10). Key IHC stains are shown in the table. Conclusions: This cohort of CUP or uncertain diagnoses with a molecular cancer classification of malignant mesothelioma, we found huge variability and critical gaps in pathological work-up. Integration of molecular cancer classification using the 92-gene assay helped resolve this diagnostic uncertainty, further supporting its clinical utility to complement standard pathology. The impact of these findings goes beyond just MPMe and may benefit numerous pts with orphan cancers, who account for nearly 20% of all cancers diagnosed globally. Research Sponsor: None.
Unveiling prognosis and traits of dMMR/MSI-H gastric and colorectal cancer after curative surgery: A large-scale, multi-center, retrospective study in China.

Background: This study conducted a large-scale multi-center analysis using real-world data from China to comprehensively investigate the clinical characteristics and prognosis of patients with deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) gastric and colorectal cancer undergoing curative surgery. Additionally, we analyzed post-operative adjuvant treatment effects and recurrence/metastasis patterns.

Methods: We retrospectively analyzed 1800 gastric and colorectal cancer patients with dMMR and/or MSI-H confirmed by immunohistochemistry (IHC) and PCR after radical resection from 19 hospitals in China. We compared clinical characteristics among positive patients identified by both testing methods and evaluated their relationship with disease-free survival (DFS) and overall survival (OS).

Results: The cohort included 1702 dMMR patients (regardless of MSI status), 667 MSI-H patients (regardless of MMR status), and 46 cases with inconsistent MMR and MSI statuses. No significant differences in overall clinical-pathological characteristics were observed between dMMR and MSI-H patients, highlighting the clinical utility of both approaches. Predominantly, MMR protein defects involved MLH1/PM2 loss (>70%). We found a positive correlation between lymph node metastasis and MLH1/PM2 protein deficiency (P < 0.01) and an inverse correlation trend in cases of MSH2/MSH6 deficiency (P < 0.1). Additionally, poorer prognosis was linked to alcohol consumption (DFS: P < 0.001), lymph node metastasis (DFS: P < 0.001; OS: P < 0.001), vascular cancer emboli (OS: P < 0.001), and neural invasion (OS: P < 0.001). In the dMMR/MSI-H colorectal subgroup, colon cancer patients exhibited superior DFS compared to rectal cancer (P = 0.025) and improved DFS with right colon tumors (P < 0.01). Patients with MLH1/MSH6 deficiency tumor showed a trend towards better survival, even within the subgroup receiving adjuvant chemotherapy (P = 0.067), compared to MLH1/PM2 and other deficiency disorders. Notably, patients with dMMR and/or MSI-H exhibited a shorter DFS following adjuvant therapy (P < 0.001), while OS did not achieve a significant difference, potentially due to the insufficient follow-up duration. Conclusions: This study provides valuable insights into the correlation between MSH2-MSH6 status and clinical characteristics in Chinese patients with gastric and colorectal cancer after radical resection. The findings also illuminate prognostic factors impacting DFS and OS, as well as the intricate relationship between the two tumor types. It highlights the feasibility of utilizing both MSH2-MSH6 and MSI-H/PCR for patient selection and enhances our understanding of the clinical management and outcomes of patients with dMMR/MSI-H gastric and colorectal cancer. Research Sponsor: None.

Patient-reported outcomes: The unmet needs of the gastrointestinal cancer community.

Background: According to the World Health Organization International Agency for Research on Cancer, gastrointestinal (GI) cancers account for 1 in 4 cancer cases and 1 in 3 cancer-related deaths worldwide. An estimated 4.8 million new cases of GI cancers and over 2 million deaths annually are reported. We performed a 12-month patient-reported outcomes (PRO) research project to provide evidence of symptom burden, treatment adherence, and recovery in GI cancer patients. This study aimed to assess the impact of PRO on clinical care, patient access to the clinical team, and enhancing patient access to the clinical team.

Methods: Our 12-month patient-reported outcomes (PRO) research included an online anonymous survey, individual and small group interviews, focus groups, advisory boards, and an interactive workshop at the 2023 American Society of Clinical Oncology annual meeting. 1,122 participants participated during this 12-month PRO research period. Participants reported being diagnosed with one of the following GI cancer primary tumor types: Anus (3%), Appendix (2%), Bile Duct (6%), Colon (19%), Esophagus (7%), Gallbladder (5%), Gastric (14%), GI NET / GI Carcinoid Tumor (3%), Liver (7%), Pancreas (6%), Small Intestine (4%), Rectum (23%), Unknown primary location (1%).

Results: Overarching areas of unmet need include: health disparities throughout the care continuum for underserved populations (21%), lack of adequate precision oncology patient education, including biomarker education and testing (19%), the rise of early-age onset (EAO) in GI cancers and the unique needs of the young adult (YA) population (18%), nutritional wellness education (17%); insufficient support for family caregivers and caregiver respite services (16%) scarcity of patient-centered care and adequate patient-clinician communication (11%).

Conclusions: Our PRO research underscores the unmet needs and gaps in support services of the GI cancer community. Our global call to action includes partnering with our 100+ member organizations to amplify the patient voice and patient-lived experience, and collaboration across our community of advocates, patients, caregivers, and clinicians. Our shared call to action and continued collaboration provides a greater impact for our GI cancer community to help meet patient needs and eliminate critical gaps in services. Research Sponsor: None.

A retrospective analysis of the efficacy and safety of imatinib in elderly patients with advanced gastrointestinal stromal tumor.

Background: Gastrointestinal stromal tumor (GIST) is a rare mesenchymal tumor arising from the gastrointestinal tract, characterized by a high predominance of the elderly population. Imatinib is the standard first-line therapy for advanced GIST with a median survival of around 4 years in pivotal clinical trials. However, clinical data for the elderly population is not well known. The aim of this study is to evaluate the efficacy and safety of imatinib in the elderly population in combination with the non-elderly population.

Methods: We extracted clinical data of patients with advanced GIST treated with imatinib as first-line therapy at our institution between January 2010 and July 2023. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and adverse events (AEs) were assessed and compared between the elderly group (age: ≥70 years, E group) and the non-elderly group (age: <70 years, NE group).

Multivariable analyses were performed using Cox proportional hazard models to evaluate the prognostic significance of age groups. Results: A total of 91 patients were included in this analysis with 32 patients in the E group and 59 patients in the NE group with a median follow-up duration of 39.8 months. Patient characteristics were as follows (the E group vs. the NE group): median age 76 (70–90) vs. 54 (29–69) years, male: 50% vs. 56%, performance status 0: 19% vs. 63%, disease status (47% vs. 44%), stomach primary 44% vs. 34%, Kit mutation (exon 11: 50% vs. 61%), and maximum tumor diameter (8-cm: 66% vs. 51%). The proportion of patients with a reduced starting dose of imatinib was significantly higher in the E group (34% vs. 2%, p < 0.0001). Median PFS in the group in the NE group were 29.4 months and 90.0 months (HR=2.04, log-rank p=0.035). Median OS in the E group and the NE group were 91.5 months and not reached (HR=7.24, log-rank p=0.02). ORR was 53% in the elderly group and 66% in the non-elderly group (p=0.32). In for OS, age was not an independent prognostic factor (HR=2.09, p=0.14) with a significant independent prognostic factor of disease status (uncertable/initially metastatic vs. recurrent (reference): HR=3.58, p<0.03). The occurrence of ≥ grade 2 non-hematologic AEs was more common in the elderly group compared to the non-elderly group (78% vs. 32%, p<0.001).

Conclusions: The elderly population with advanced GIST may achieve a survival period comparable to that observed in pivotal trials with imatinib. Even with reduced doses of imatinib, careful monitoring is necessary because of the high frequency of non-hematologic ≥ grade 2 AEs in the elderly population. Research Sponsor: None.
**733 Poster Session**

Real-world effectiveness and safety of pembrolizumab in mismatch repair-deficient (dMMR) gastrointestinal non-colorectal tumors. First Author: Nieves Martinez Lago, Complejo Hospitalario Universitario de Ferrol, Ferrol, Spain.

**Background:** The KEYNOTE-158 trial demonstrated durable clinical efficacy with pembrolizumab in long-term follow-up of previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. Our study, the GAIN study, aims to evaluate effectiveness and safety of pembrolizumab in dMMR Gastrointestinal Non-Colorectal Tumors in real-world clinical practice. **Methods:** We conducted a multicenter, retrospective, observational study on patients with Mismatch Repair-Deficient (dMMR) Gastrointestinal Non-Colorectal Tumors treated with pembrolizumab in real-world practice at six university hospitals affiliated with the Galician Research Group on Digestive Tumors (GituD) in Northwest Spain. **Results:** Between January 2018 and April 2023, 35 patients were enrolled. The median age was 66 years (range 33-88), with 54.3% being female. Tumor locations included 23 (65.7%) gastroesophageal adenocarcinomas, 8 (23.4%) pancreatic adenocarcinomas, 2 (5.7%) duodenal adenocarcinomas, 2 (5.7%) intrahepatic cholangiocarcinomas, 2 (5.7%) jejunal adenocarcinomas, 2 (5.7%) esophageal squamous cell carcinomas, and 1 (2.8%) tumor of unknown origin. 54.3% of tumors were poorly differentiated. The most frequent alteration was the loss of MLH1-PM52 expression (71.4%). By tumor location, 100% of gastroesophageal, jejune, and unknown origin tumors showed MLH1-PM52 loss; while 100% of duodenal, pancreatic, and biliary tumors exhibited MSH2-MSH6 loss. All patients received pembrolizumab, with 57.1% having no prior metastatic disease treatment, 80% having ECOG PS0-1, and 31.4% having hepatic metastases. Among 33 evaluable patients, the overall response rate (ORR) was 81.8% (including 30.3% complete response) and the disease control rate (DCR) was 90.9%. Specifically, in gastroesophageal adenocarcinomas, the ORR was 94.1%, and the DCR was 95.0%. In the overall population, the median progression-free survival (PFS) was 34.76 months (95% CI 5.33 – 64.19 months), and the median overall survival (OS) was 39.75 months (95% CI 4.33-75.18 months). Treatment was well-tolerated; only 3 patients (8.6%) required discontinuation due to neuropsychiatric symptoms or arthralgia. No treatment-related deaths occurred. **Conclusions:** Our study underscores the real-world effectiveness of pembrolizumab in patients with dMMR Gastrointestinal Non-Colorectal Tumors. The high ORR, DCR, and favorable safety profile support its use in this challenging patient group, providing valuable real-world evidence for clinical decision-making. Research Sponsor: None.

**734 Poster Session**

Examining the prevalence of anxiety and depression in surgical oncology patients: Results of a prospective cohort study. First Author: Judy Li, Department of Surgery, Division of Surgical Oncology at Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** Prospective data assessing prevalence of anxiety and depression in a diverse surgical oncology population are currently lacking. Psychological distress may affect patient outcomes in the postoperative setting. The General Anxiety Disorder (GAD) and Patient Health Questionnaire (PHQ2) surveys are validated instruments to assess severity of anxiety and depression, respectively. We aimed to determine the prevalence and risk factors for anxiety and depression in surgical oncology patients. **Methods:** To assess associations between anxiety and depression with clinical outcomes in patients presenting to our surgical oncology clinic. **Methods:** A prospective, surgeon-blinded study was conducted to assess associations of anxiety and depression with postoperative outcomes in patients with gastrointestinal cancer who underwent surgical intervention. Preoperatively, the GAD and PHQ2 surveys were administered to evaluate anxiety and depression, respectively. Fruity level was also assessed using the validated Risk Analysis Index (RAI-D) survey. Postoperative outcomes included rates of ICU admission, 30- and 90-day readmissions, postoperative complications classified by Clavien-Dindo score, and disposition to home versus rehabilitation facilities. Outcomes were compared between different groups as defined by the severity of anxiety and depression. **Results:** 191 patients met inclusion criteria. The cohort was stratified into three groups by severity of anxiety and depression. Overall, 59 (31%) patients reported at least moderate anxiety as defined by a GAD score ≥5, with 30 (15.7%) patients reporting severe anxiety (GAD score > 10). Similarly, 62 (32%) patients reported at least mild depression as defined by a PHQ2 score ≥ 5, with 11 (5.7%) patients experiencing moderate to severe depression (PHQ9 > 10). No difference was detected in length of stay, ICU admission, 30- and 90-day readmission, and postoperative complications. Preoperative frailty, as defined by RAI-D score > 21, was also not associated with anxiety or depression. **Conclusions:** Our study underscores the remarkable response rates and durability of pembrolizumab monotherapy in 40 (80%) patients, ileal, or nivolumab in 8 (16%), and nivolumab plus chemotherapy in 2 (4%) patients. Most patients, 33 (66%), were treatment-naïve. The median duration of NIT was 6 months (range: 1.5 to 55), with a time to best response of 3 months (range: 1.5 to 12). Among 47 evaluable patients, the best responses were as follows: an overall response rate of 75% (35/47), consisting of radiologic complete response and partial response of 20% (9/47). The median progression-free survival and overall survival were not reached after a median follow-up of 14 months (range: 2-80), calculated from the date of the first immunotherapy dose to the last follow-up or death. Among 24 patients achieving CR, all remained progression-free after a median follow-up of 14 months (range: 2-80), calculated from the date of the first immunotherapy dose to the last follow-up or death. Among 24 patients achieving CR, all remained progression-free after a median follow-up of 25.5 months (range: 3-80). Stable and progressive diseases were observed in 7 (15%) and 5 (10%) patients, respectively. Only 5 (10%) patients underwent surgery following NIT, with 4 (80%) achieving pathologic CR. The reasons for not proceeding with surgery were comorbidities in 40 (80%) patients, disease extent in 4 (8%), and patient refusal in 1 (2%). Out of the 12 patients who expired at the data cut-off, 1 was due to immunotherapy-related pneumonia, 6 due to disease progression, and the remainder from underlying comorbidities. **Conclusions:** Overall, NIT achieved durable responses in 40 (80%) patients with dMMR/MSI-H GI cancers. Progression on NIT was infrequent. These real-world data support further investigation into non-operative approaches for patients with dMMR/MSI-H GI cancers. Research Sponsor: None.

**735 Poster Session**

Liquid biopsy-based comprehensive genomic profiling to reveal mutational landscape in real-world patients with gastrointestinal cancer. First Author: Haoran Tang, Huidu Shanghai Medical Sciences, Ltd., Shanghai, China.

**Background:** Molecular characteristics hold substantial clinical significance in cancer. Previous research has elucidated the molecular classification of gastrointestinal (GI) cancers, leveraging microsatellite instability, chromosomal instability, and chromosomal abnormalities. However, most of these studies relied on tissue biopsies. Limited investigations have been documented regarding the characterization of molecular profiles through liquid biopsy. Here we present a comprehensive genomic profiling study conducted on advanced GI cancer patients using blood samples. **Methods:** This prospective study is a part of a global initiative focused on molecular biomarker screening across various solid tumors. Here we report the early result of 106 unresectable GI cancer patients, encompassing those with advanced disease or experiencing relapse after prior treatments. The cohort comprises 66 colorectal cancer (CRC) patients, 34 gastric cancer (GC) patients, and 6 esophageal cancer (EC) patients. Each patient contributed a 10-mL blood sample for comprehensive circulating tumor DNA (ctDNA) analysis. The study employed PredicineDARE, a 152-gene, NGS-based liquid biopsy assay, to profile somatic gene variations within this patient population. **Results:** The study revealed a total of 1,597 somatic mutations, with 1,077 occurring in CRC. **Conclusions:** The current study establishes a comprehensive genomic profiling strategy to provide crucial insights into the outcomes, safety profile, and response patterns of dMMR/MSI-H GI cancer patients undergoing NIT. Herein, we present the initial findings. **Methods:** We developed a centralized database to collect de-identified clinical data from patients with dMMR/MSI-H GI cancers receiving NIT. We collected data retrospectively and prospectively through September 15, 2023. **Results:** The current report includes 50 patients with a median age of 67 years (range 32 to 90); 21 (42%) were female, 18 (36%) were male, and the remaining were White. The cohort included the following tumor types: 31 (62%) colorectal, 7 (14%) gastroesophageal, and 12 (24%) pancreaticobiliary. Most patients had localized disease (34, 68%), while the rest had oligometastatic disease. NIT consisted of pembrolizumab monotherapy in 40 (80%) patients, ipilimumab plus nivolumab in 8 (16%), and nivolumab plus chemotherapy in 2 (4%) patients. Most patients, 33 (66%), were treatment-naïve. The median duration of NIT was 6 months (range: 1.5 to 55), with a time to best response of 3 months (range: 1.5 to 12). Among 47 evaluable patients, the best responses were as follows: an overall response rate of 75% (35/47), consisting of radiologic complete response (CR) in 20 (43%), pathologic CR in 4 (9%), and partial response in 11 (24%). The median progression-free survival and overall survival were not reached after a median follow-up of 14 months (range: 2-80), calculated from the date of the first immunotherapy dose to the last follow-up or death. Among 24 patients achieving CR, all remained progression-free after a median follow-up of 25.5 months (range: 3-80). Stable and progressive diseases were observed in 7 (15%) and 5 (10%) patients, respectively. Only 5 (10%) patients underwent surgery following NIT, with 4 (80%) achieving pathologic CR. The reasons for not proceeding with surgery were comorbidities in 40 (80%) patients, disease extent in 4 (8%), and patient refusal in 1 (2%). Out of the 12 patients who expired at the data cut-off, 1 was due to immunotherapy-related pneumonia, 6 due to disease progression, and the remainder from underlying comorbidities.
Characteristics and predictors of outcomes with neoadjuvant imatinib in gastrointestinal stromal tumors: Real-world data from a large patient registry. First Author: Udhayir Singh Grewal, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: The standard of care for patients with moderate or high-risk resectable gastrointestinal stromal tumors (GIST) is surgical resection followed by adjuvant therapy with imatinib. The impact of neoadjuvant imatinib on long-term outcomes is largely unknown.

Methods: We leveraged the LifeRaft registry, a large international open cohort of patients with GIST. We included patients who did not have metastatic disease at diagnosis, underwent surgical resection and received neoadjuvant imatinib and had no recorded mutations of Kit exon 13 or PDGFRα exon 18 D842V. Baseline patient characteristics were described and survival probabilities were estimated and plotted using the Kaplan-Meier method. Cox regression was used to estimate the effect of demographic and clinical characteristics on recurrence-free survival (RFS) and overall survival (OS). For RFS, time was calculated from the date of surgery to disease recurrence/death, whichever came first. For OS, time was calculated from the date of surgery to death. Estimated effects of predictors were reported as hazard ratios (HR) along with 95% confidence intervals (CI). All statistical testing was two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC).

Results: Out of 2,472 patients with GIST, 137 patients met the inclusion criteria and received neoadjuvant imatinib for a median of 6.8 months. Majority of the patients were aged 40 years or above (129/137, 94.2%) and were males (73/137, 53.3%). The majority of the patients had gastric GIST (72/137, 54.1%), followed by small intestine GIST (34/137, 25.6%) and other (27/137, 20.3%). Most patients had a tumor size of >10 cm (66/137, 52.4%) at the time of diagnosis followed by >5 cm (41/137, 30.3%) and <2 cm (16/137, 14.3%). The median RFS for the cohort was 6.1 years. On multivariable analysis, tumor size (HR 1.08, 95% CI 1.05-1.12, p=0.001) and duration of therapy (HR 0.98, 95% CI 0.97-0.99, p=0.01) were significantly associated with RFS. A 1-cm increase in tumor size and 1-month increase in total time on imatinib was associated with an 8% increase and 2% decrease in risk of recurrence. The median OS was 14.2 years. Female gender (HR 0.23 95% CI 0.08-0.65, p=0.001) and total length of time on imatinib (HR 0.97 95% CI 0.96-0.99, p<0.01) were found to be significantly associated with OS. Female patients were associated with a 77% decreased risk of death and a 1-month increase in the total time on imatinib was associated with a 2% decrease in risk of death. In our cohort, 61.3% of patients received surgery within 24 months of diagnosis, and 81.4% of patients received surgery after 24 months of diagnosis. In the cohort, 48.4% of patients received neoadjuvant imatinib and had gastric GIST with tumor size >10 cm. Smaller tumor size and female gender predicted longer RFS and OS respectively. Longer total duration of imatinib therapy was associated with increased RFS and OS. 

Conclusions: To our knowledge, this is the first real-world report about anlotinib for gastrointestinal tumors with liver metastases in China, showed the clinical benefit of anlotinib in a specific time period for this patient population.
Role of proton pump inhibitors in immune checkpoint inhibitor colitis. First Author: Roshini Pradeep, Midwestern University GME Consortium Residency Program, Cottonwood, AZ

Background: Proton pump inhibitors (PPIs) are known to be beneficial in symptomatic control of gastrointestinal reflux disease and gastritis which can be a common complication of various cancers specifically gastrointestinal (GI) cancers. Microscopic colitis development has been studied to be associated with PPI use. Immune checkpoint Inhibitor (ICI) colitis is a known adverse effect of Inhibitors of Programmed cell death 1 (PD-1) and its ligand (PD-L1). Previous studies have also shown use of PPIs and NSAIDs are common risk factors which can exacerbate ICI Colitis caused by Inhibitors of PD-1 and PD-L1. This study is designed to observe association of certain drugs especially PPIs in ICI colitis.

Methods: This is a single center, retrospective, and observational study that investigated patients treated with PD-1 and PD-L1 Inhibitors for management of any type of cancer between January 2022- September 2023. A list of patients treated with PD-1 and PD-L1 inhibitors was obtained from Inpatient pharmacy records followed by retrospective chart review to look for symptoms of colitis and other medications used by each patient. Primary outcome was to observe the role of PPIs in ICI colitis.

Secondary outcomes were to observe the number of patients with GI cancers on PPIs who developed colitis. We also observed the effect of NSAIDs usage were categorized as compliant. Among this group, there was a significant increase in body mass index (P=0.005). Handgrip measurements for assessing muscle strength demonstrated a statistically significant increase, with handgrip weight rising from 24.9 ± 8.9 kg at the first visit to 26.7 ± 9.5 kg at the third visit (P=0.005). ONS-compliant patients also showed statistically significant improvements in weight, total body water, basal metabolic rate, and calf circumference measurements. The proportion of ONS-compliant patients decreased from 80.5% (n=343) at the first visit to 62.4% (n=93) at the third visit. Additionally, a statistically significant improvement was observed in food consumption records (P=0.004). In assessments using the EORTC QLQ-C30, there were significant improvements noted in general health status, fatigue, pain, and insomnia scales, as well as in physical, emotional, and social functioning. A significant difference was identified between visits 1 and 2 in PSQI scores using 0.001. A secondary endpoint was to observe the effect of PPI use in muscle strength, anthropometric measurements, and quality of life data. The importance of addressing malnutrition in patients with GI cancer cannot be overstated. Therefore, it is imperative to maintain regular monitoring of their nutritional status and adherence to ONS. Research Sponsor: None.

Immune-related adverse events in patients with gastrointestinal cancer undergoing pembrolizumab monotherapy: A systematic review of clinical trials. First Author: Nikolaos Naleid, Department of Internal Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH

Background: Pembrolizumab, an immune checkpoint inhibitor targeting programmed death 1 (PD-1) and its ligand programmed death ligand 1 (PD-L1), is widely employed in the treatment of various gastrointestinal (GI) cancers. This systematic review aims to assess the spectrum and incidence of immune-related adverse events (irAEs) associated with pembrolizumab monotherapy in GI cancer patients. Two independent authors reviewed the articles and extracted data, with discrepancies resolved by consensus. Primary endpoints included the incidence of grade 3 or higher irAEs and the treatment discontinuation rate due to irAEs. Secondary endpoints encompassed the incidence of any-grade irAEs and specific irAEs such as pneumonitis, colitis, hepatitis, myositis, myocarditis, nephritis, pancreatitis, peripheral neuropathy, skin toxicity, endocrine toxicity, infusion reactions, and deaths.

Methods: A comprehensive search of PubMed/MEDLINE was conducted to identify full-text articles of clinical trials investigating pembrolizumab monotherapy in GI cancer patients. Two independent authors reviewed the articles and extracted data, with discrepancies resolved by consensus. Primary endpoints included the incidence of grade 3 or higher irAEs and the treatment discontinuation rate due to irAEs. Secondary endpoints encompassed the incidence of any-grade irAEs and specific irAEs such as pneumonitis, colitis, hepatitis, myositis, myocarditis, nephritis, pancreatitis, peripheral neuropathy, skin toxicity, endocrine toxicity, infusion reactions, and deaths.

Results: After excluding duplicates and articles not meeting inclusion criteria, data extraction and analysis were performed on 25 selected articles. Common reasons for exclusion included concomitant use of chemotherapy or targeted therapy and trials involving non-GI cancer patients. The analysis included 2866 patients with a median age of 62 years, of which 29% were female. Tumor types included colorectal (13%), esophageal (46%), hepatocellular carcinoma (25%), and others (16%). The aggregate incidence of grade 3 or higher irAEs was 8.7%, with reported rates ranging from 3% to 41% across different trials. The incidence of any grade irAEs varied from 3% to 98%. The treatment discontinuation rate due to irAEs was 6.8%. The most common grade 3 or higher irAEs were pneumonitis (3.3%), hepatitis (2.3%), colitis (0.7%), and nephritis (0.7%). irAE-related deaths were infrequent (0.9%). Detailed irAE data are summarized in the Table. Conclusions: In GI cancer patients receiving pembrolizumab monotherapy, severe irAEs are rare. Treatment discontinuation and deaths attributed to pembrolizumab-related irAEs are infrequent, underscoring the safety profile of this therapy in patients with GI cancer. Research Sponsor: None.

<table>
<thead>
<tr>
<th>irAE</th>
<th>Any Grade (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>96/2866 (3.3%)</td>
<td>24/2866 (8%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>54/2866 (1.9%)</td>
<td>20/2866 (0.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>156/2866 (8.2%)</td>
<td>10/2866 (0.3%)</td>
</tr>
<tr>
<td>Myositis</td>
<td>14/2866 (0.5%)</td>
<td>3/2866 (0.1%)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>2/2866 (0.07%)</td>
<td>1/2866 (0.03%)</td>
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<tr>
<td>Skin rash</td>
<td>196/2866 (6.8%)</td>
<td>11/2866 (0.4%)</td>
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<tr>
<td>Hypothyroidism</td>
<td>357/2866 (9.8%)</td>
<td>2/2866 (0.1%)</td>
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<tr>
<td>Adrenal insufficiency</td>
<td>17/2866 (0.6%)</td>
<td>6/2866 (0.21%)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>19/2866 (0.6%)</td>
<td>0/2866 (0.0%)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>27/2866 (0.9%)</td>
<td>0/2866 (0.0%)</td>
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Visit meetings.asci.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase Ib adaptive study of datatinib for the prevention of oxaliplatin-induced neuropathy in patients with gastrointestinal (GI) cancers receiving FOLOFOX chemotherapy with or without bevacizumab. First Author: John Raymond Zalcberg, Dana Farber Cancer Institute/Brigham and Women’s Hospital Cancer Center, Boston, MA

Background: Neurotoxicity is one of the most significant and disabling side effects of oxaliplatin (OX) and frequently limits the amount of OX that can be used. OX uptake by organic cation transporter 2 (OCT2) into mouse and rat dorsal root ganglia is a prerequisite for OX-induced peripheral neuropathy (OPIN). Preclinical data in rat and mouse models from our group showed that by inhibiting YES1, pre-treatment with datatinib (D) inactivated OCT2 and prevented acute and chronic OPIN. A phase I trial is ongoing investigating addition of D prior to OX to prevent OPIN. Methods: This was a Bayesian Phase Ib dose-finding study with adaptive dose selection using efficacy-toxicity trade-offs in patients (pts) with GI cancers where all candidates for mFOLOFOX + bevacizumab [NCT04164069]. Pts received chemotherapy on day 1 and 15 schedule, every 28 days. D was administered at one of 2 dose levels of NMN, and 3/7 pts had prior lines of treatment by INV, and 2 pts discontinued due to treatment-related AEs per INV. Conclusions: In the first phase of D, it was shown that datatinib prophylaxis was safe and well tolerated in pts with metastatic colorectal cancer (mCRC) and that D was feasible to use prior to each dose of FOLOFOX on screening through to day 0 of cycle 1. Weakly informative Jeffreys priors were used for response and toxicity probabilities, with the latter constrained to be increasing with dose. Results: 13 pts were screened. 5 pts enrolled in cohort 1 (D 100mg), 2 in cohort 2 (D 104mg) and 2 in cohort 3 (D 140mg). 6 pts were not evaluable for efficacy and toxicity endpoints due to screen failure or early study discontinuation. 7 patients were evaluated for efficacy biomarkers and 6 pts were evaluated for both efficacy biomarkers and toxicity. There were no DLTs observed in any cohort. 4/7 pts had ≥2-fold increase in AUC of OPIN but no change in AUC of OCT2. 6/7 pts had <20% change in the clearance of OX. Conclusions: Addition of D 100mg or 140mg to traditional FOLOFOX regimen was safe and in the majority of pts appeared to alter serum biomarkers of OPIN in a manner suggesting inhibition of OX uptake in the DRG. 140mg was chosen as the RP2D. A randomized controlled trial using blinded D vs placebo will be performed. Clinical trial information: NCT04164069. Research Sponsor: Pelotonia Intramural Research Program; Noonan_Hu

Dastatinib Dose 100 mg (95% CI) 140 mg (95% CI)
Estimated response probability 38% (3.9% to 82.5%) 50% (12.4 to 87.9%)
Estimated toxicity probability 9% (0 to 33.4%) 14% (0.4% to 45.7%)

Overall survival and long-term safety with ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib: Final analyses from INTRIGUE. First Author: John Raymond Zalcberg, School of Public Health and Preventative Medicine, Monash University, and Alfred Health, Melbourne, Australia

Background: Ripretinib is a switch-control tyrosine kinase inhibitor approved for patients (pts) with gastrointestinal stromal tumor (GIST) who received prior treatment with 3 or more kinase inhibitors, including imatinib. Sunitinib is approved for advanced GIST after imatinib failure. In the second interim analysis of the phase III INTRIGUE (NCT03673501) trial, OS was similar between treatment arms. The safety profile remained consistent and more favorable for ripretinib vs sunitinib in pts with advanced gastrointestinal stromal tumor (GIST) who had disease progression on or intolerance to imatinib. Randomization was 1:1 to the 2 ITT populations (Table). Fewer pts had grade 3/4 treatment-emergent AEs with ripretinib vs sunitinib (3% vs 6%). There were 211 OS events (47%) in the AP ITT population with CNS activity, is approved in multiple countries for the treatment of RET-rearranged thyroid as well as RET-rearranged non-thyroid malignancies. Methods: The ongoing clinical trial (NCT04727151) is an open-label, phase 3 study of adults with advanced RET+ cancers across multiple tumor types and fusion partners, including difficult-to-treat GI cancers with poor results in standard-of-care options, such as pancreatic and colorectal. These results emphasize the importance of comprehensive genomic profiling across all tumor types in order to identify actionable oncogenic drivers, including RET fusions. Clinical trial information: NCT06373501. Research Sponsor: Deciphera Pharmaceuticals

Final OS analysis.

<table>
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<tr>
<th>Events, number of patients</th>
<th>N = 327</th>
<th>HR (95% CI)</th>
<th>35.5 vs 32.8, 3 years</th>
<th>3.48 (2.95 to 4.11)</th>
<th>0.98 (0.71 to 1.34)</th>
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<tbody>
<tr>
<td>OS rate, %</td>
<td>1 year</td>
<td>75 ± 4 vs 76</td>
<td>0.86 (0.65 to 1.13)</td>
<td>0.58 (0.37 to 0.89)</td>
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<tr>
<td></td>
<td>2 years</td>
<td>75 ± 4 vs 76</td>
<td>0.86 (0.65 to 1.13)</td>
<td>0.58 (0.37 to 0.89)</td>
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<tr>
<td></td>
<td>3 years</td>
<td>75 ± 4 vs 76</td>
<td>0.86 (0.65 to 1.13)</td>
<td>0.58 (0.37 to 0.89)</td>
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Data cutoff: March 15, 2023. CI, confidence interval; HR, hazard ratio; median, median.

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
SBRT with ipilimumab and nivolumab to metastatic MSS colorectal and pancreatic cancer: A pooled analysis of four prospective phase II trials. First Author: Hannah Johnson Roberts, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA

Background: The role of immunotherapy (IO) in metastatic stable (MSS) colorectal and pancreatic cancer is limited. Stereotactic body radiation therapy (SBRT) is increasingly used in the limited metastatic setting, however its use with IO requires an area of investigation for both target response and overall systemic response. Here we evaluate the local failure rate of irradiated target lesions with and without IO. Methods: We pooled four prospective phase II single-arm studies of patients with metastatic MSS colorectal or pancreatic cancer treated with SBRT alone or with IO. Those in the first study (NCT01239381) received ablative liver SBRT to a maximum biologically effective dose (BED) of 48-100 Gy. Patients in the remaining studies received low dose SBRT to liver, lung, or nodal metastases with 24 Gy in 3 fractions to a BED of 43.2 Gy in combination with Ipilimumab and Nivolumab during the first (NCT04561162, NCT04579592) or second (NCT03104439) cycles. Local failure rates at the time of first progression were estimated by the cumulative incidence with non-target progression only and death as competing risks and compared using Gray's test. The best response at the target was measured with the RECIST 1.1 criteria using the largest reduction in target size during follow-up. Fisher's exact test was used to compare objective response (ORR) and disease control rates (DCR), while the Wilcoxon rank sum test was performed to compare target size and percentage of tumor reduction. Results: Across all four studies there were 154 evaluable patients including 50 who received ablative SBRT and 104 patients who received low dose SBRT with IO. There were 92 patients with colorectal and 62 with pancreatic cancer. Median target size was 3.7 cm in the ablative SBRT group and 2.8 cm in the IO group (P=0.04). The 6-month, 1-year, and 2-year local failure rates were 10%, 18%, and 20% respectively following ablative SBRT and 24%, 25%, and 26% following low dose SBRT with IO (P=0.03). The ORR was 50.0% with SBRT alone and 23.1% with the addition of IO (P=0.001). There was no significant difference in the DCR (80.0% vs. 68.3%, P=0.18). The percent decrease in size was significantly higher in those with ablative SBRT (median -53.0% vs. -10.6%, P=0.02). There was no difference in the ORR and DCR between subject and patients treated with IO (P=0.13) KHT with a lymphocyte to CD8 ratio of 0.35 (TPS=0.27) status. Conclusions: Despite the use of low dose SBRT with immune checkpoint inhibitors, there was no significant difference in local failure rates compared to ablative SBRT. Ablative SBRT dosing yielded a significantly higher depth of response. As clinical and molecular studies suggest higher metastases are less responsive to radiation and fractionation schemas for optimal local control is critical. Further studies are needed to explore the radiation dose with regards to local control when delivered with IO.

Efficacy of biomarker-matched therapy in clinical trials for advanced gastrointestinal cancers: A pooled analysis of SCRUM-Japan studies. First Author: Tadayoshi Hashimoto, Department of Gastroenterology and Gastrointestinal Oncology/Translational Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan

Background: We conduct the SCRUM-Japan MONSTAR-SCREEN, a nationwide molecular profiling project to facilitate the enrollment of patients with advanced solid tumors into matched clinical trials based on identified biomarkers. Here, we investigated clinical outcomes of patients with gastrointestinal cancers in this project. Methods: The SCRUM-Japan GI SCREEN was launched for gastrointestinal cancers in 2015, followed by MONSTAR-SCREEN for lung, breast, and other cancers in 2016. The used profiling assay for genomic alterations was Oncomine Comprehensive Assay for tumor tissue in GI SCREEN, Guardant360 for plasma in GOZILA, FoundationOne CDx for tissue and FoundationOne Liquid CDx for plasma in MONSTAR-SCREEN-1, and CARIS MI Profile for tissue in MONSTAR-SCREEN-2. Patients were treated in clinical trials or practice based on identified biomarkers. We analyzed data from patients with gastrointestinal cancers in this project. Results: Of 11,408 patients enrolled in our project as of May 22, 2023, 555 (5.0%) were enrolled in matched clinical trials based on identified biomarkers. The major cancer types that had matched clinical trials included colorectal (63.2%), biliary tract (12.4%), gastric (9.2%), esophagus (6.5%), and pancreatic cancer (4.7%). The objective response rate (ORR), median progression-free survival, and median overall survival (OS) for patients in matched trials were 27.8% (95% CI, 24.0% to 31.9%), 3.0 months (95% CI, 2.8 to 3.7 months), and 14.4 months (95% CI, 13.0 to 16.1). The major treatment lines in which investigational drugs were administered were third (24.6%) and fourth (16.0%) line. Evaluating by each drug target given at least 20 patients, therapies targeting HER2 had the highest ORR of 46%, followed by PD-1/PD-L1 (33%), BRAF (30%), and MEK (28%). Antibody-drug conjugates demonstrated the highest ORR with 48.8%, followed by monoclonal antibodies at 37.7% and small molecule inhibitors at 23.0%. Overall, patients who received matched therapy in clinical trials or practice had significantly longer OS than those who did not (hazard ratio, 0.76; 95% CI 0.69 to 0.84; P<0.001). Our findings demonstrate that coordinated enrollment project has facilitated the enrollment of patients with advanced gastrointestinal cancers in clinical trials. Furthermore, it demonstrated a survival benefit by providing patients matching targeted therapy. Research Sponsor: None.
Is lymph node metastasis an event indicating an advanced gastrointestinal stromal tumor? First Author: Peng Zhang, Wuhan Union Hospital, Wuhan, Hubei, China

Background: The clinicopathological features and prognosis of gastrointestinal stromal tumors (GISTs) metastasizing to lymph node are controversial owing to their low incidence. A multicenter retrospective cohort study was conducted to compare the clinicopathological features and oncologic outcomes of GIST with and without lymph node metastases.

Methods: The medical records of patients with GISTS in 16 large medical centers in China from January 2014 to December 2020 were reviewed. Patients were divided into three groups: no metastasis, lymph node metastasis without distant metastasis, and distant metastasis without lymph node metastasis. Propensity score matching (PSM) was performed to reduce confounding factors. Results: A total of 1109 cases of primary GIST were included in this study, comprising 607 males (54.7%) and 502 females (45.3%), with a mean age of 56.6±11.9 years. There were 1024 patients (92.3%) with no lymph node metastasis after surgery, and 85 patients (7.7%) had lymph node metastasis. Compared to that in GIST without lymph node metastasis, the proportion of non-gastric GIST was higher in GIST with lymph node metastasis (52.9% vs. 40.7%) with a larger tumor diameter (>10 cm: 36.5% vs. 18.1%) and more patients with distant metastasis (11.8% vs. 3.5%). Tumor location not in the stomach, the largest tumor diameter, and distant metastasis were independent risk factors for GIST with lymph node metastasis (all P < 0.05). After PSM, 96, 48, 24 patients comprised no metastasis, lymph node metastasis without distant metastasis, and distant metastasis without lymph node metastasis, respectively. The relapse-free survival (RFS) of the lymph node metastasis group was comparable to that of the distant metastasis group without lymph node metastasis (P = 0.368) and significantly inferior to that of no metastasis (P = 0.004).

Conclusions: The prognosis of patients with GIST with lymph node metastasis was comparable to that of patients with distant metastasis and significantly worse than that of patients without metastasis. Lymph node metastasis may be an advanced event in GIST. Research Sponsor: None.

Comprehensive genomic profiling of squamous cell carcinoma of unknown primary presenting with liver metastases. First Author: Hannah Ruth Robinson, University of Colorado Cancer Center, Aurora, CO

Background: Carcinomas of unknown primary (CUPs) are comprised of metastatic cancers for which a primary tumor of origin cannot be identified despite a full diagnostic workup. They frequently present with liver metastases, which portend a poor prognosis. Strategies employing comprehensive genomic profiling (CGP) to identify targeted treatments for CUPs have shown potential. Despite this, the molecular landscape of squamous cell carcinomas of unknown primary (SCCUPs) remains poorly defined. This study describes the results of CGP testing in patients with SCCUPs detected at the Foundation Medicine, Inc. database, with a focus on those with liver involvement.

Methods: Cases of SCCUPs with FoundationOne CDx (F1CDx) assay results were identified based on a reported diagnosis of CUP and the presence of SCC histology. Cases then underwent central pathologist review and were excluded if a known primary site could be determined based on histology and disease location. Cancer patients with liver involvement were selected based on the site of tissue biopsy. Genomic analyses of identified cases were assessed using the FoundationCORE database. Results: Sixty-nine cases of SCCUP presenting with liver involvement were identified. Alterations were observed in 102 of 324 (31.5%) genes evaluated by the F1CDx assay in at least 1 patient. The most frequently altered genes were TP53 (66.7%), CDKN2A (33.3%), CDKN2B (23.2%), KRAS (21.7%), PIK3CA (18.8%), NF2EL2 (11.6%), SOX11 (12.6%), M2M2 (10.1%), and MTAP (10.1%). No patients had microsatellite instability-high disease, only 6 (8.7%) patients had a tumor mutational burden (TMB) > 10, and 11 (15.9%) patients had evidence of HPV infection. Among 33 patients with available PDL-1 testing results, 7 (21.2%) had high-expression positive. An additional 574 cases of SCCUP were identified with involvement outside of the liver. Compared to these cases, patients presenting with liver involvement had less genomic alterations per tumor (5.10 vs 6.71, p=0.005), and were less likely to have TMB > 10 (8.7% vs 38.0%, odds ratio [OR] 0.16, p<0.001). KRAS mutations were observed in 17% of the representing 8.3% of other SCCUP patients (OR 3.07, p=0.07). Conclusions: SCCUPs presenting with liver metastases had reduced numbers of genomic alterations and decreased TMB compared to other SCCUPs, suggesting these tumors may be less likely to respond to immunotherapy. Despite this, 36.2% of these patients had at least one alteration that could potentially guide targeted therapies into future treatment decisions including enrolling patients in targeted-driven clinical trials. Interestingly, there was a trend toward increased KRAS alterations in those with liver metastases. To our knowledge, this is the first report that describes the genomic landscape of SCCUPs presenting with liver metastases. Research Sponsor: None.

Clinical validation of Northstar Response, a novel methylated ctDNA therapy response monitoring assay in patients with advanced GI cancer undergoing active treatment. First Author: Ilyas Sahin, University of Florida/UF Health Cancer Center, Gainesville, FL

Background: ctDNA is an invasive way to holistically assess the tumor. Several assays developed for therapy response monitoring rely on variant allele frequencies to detect scarce somatic variants in the blood. In contrast, methylated ctDNA measurement has shown promise as a treatment monitoring biomarker without requiring a tumor biopsy, yet accuracy is limited in ability to precisely quantify the amount of methylation present in the ctDNA.

Methods: This prospective, observational study assesses the clinical validity of Northstar Response, a quantitative methylated ctDNA therapeutic response monitoring assay that does not require prior tumor tissue. A cohort of 100 advanced cancer patients with a variety of GI malignancies were tested positive for ctDNA while 37.5% had undetectable ctDNA despite having residual disease, 38% had positive ctDNA while out of 25% with no radiographically metastatic disease, 10 out of 31 patients were alive but one out of two ctDNA positive patients had a relapse at 39 months follow-up. Kotthis et al. 2022 reported 51% ctDNA positivity and 11% had longitudinal ctDNA measurements available which correlated well with their disease course. Zeineddine et al. 2023 collected 160 blood samples from 147 patients. Of 75% with radiographically metastatic disease, 38% was positive for ctDNA while 37.5% had undetectable ctDNA despite having residual peritoneal disease and 25% had insufficient DNA from tumor specimen. Lopez-Rojo et al. 2020 reported 50% ctDNA positive rate. All included patients had KRAS mutation and received hyperthermic intraperitoneal chemotherapy (HIPEC). On 35.6 months follow-up all the patients were alive but one out of two ctDNA positive patients had a relapse at 39 months follow-up.

Conclusions: Following PRISMA guidelines, PubMed, Cochrane, and Clinicaltrials.gov were searched for ‘Appendiceal Neoplasms’ AND Circulating Tumor DNA. Four original studies reporting the role of ctDNA in appendiceal cancer were included after screening 195 articles. A total of 196 patients were included in the review. (Table) The total number of collected samples was 209 and 41% were tested positive for ctDNA. Singh et al. 2023 reported eight stage IV appendiceal cancer patients with the median age of 64.5 (45-75) years. 37.5% was positive for ctDNA while 37.5% had undetectable ctDNA despite having residual disease, 25% had insufficient DNA from tumor specimen. Lopez-Rojo et al. 2020 reported 50% ctDNA positive rate. All included patients had KRAS mutation and received hyperthermic intraperitoneal chemotherapy (HIPEC). On 35.6 months follow-up all the patients were alive but one out of two ctDNA positive patients had a relapse at 39 months follow-up. Kotthary et al. 2022 reported 51% ctDNA positivity and 11% had longitudinal ctDNA measurements available which correlated well with their disease course. Zeineddine et al. 2023 collected 160 blood samples from 147 patients. Of 75% with radiographically metastatic disease, 38% was positive for ctDNA while 37.5% had undetectable ctDNA despite having residual peritoneal disease and 25% had insufficient DNA from tumor specimen. Lopez-Rojo et al. 2020 reported 50% ctDNA positive rate. All included patients had KRAS mutation and received hyperthermic intraperitoneal chemotherapy (HIPEC). On 35.6 months follow-up all the patients were alive but one out of two ctDNA positive patients had a relapse at 39 months follow-up. Kotthary et al. 2022 reported 51% ctDNA positivity and 11% had longitudinal ctDNA measurements available which correlated well with their disease course.

Conclusions: The use of ctDNA in metastatic appendiceal tumor is not widespread and detection rates are heterogenous. It was observed more in poorly differentiated appendiceal cancers but further studies are needed to evaluate its utility in clinical practice. Research Sponsor: None.

Circulating tumor DNA positivity in metastatic appendiceal neoplasms: A systematic review. First Author: Moazzam Shahzad, University of South Florida/ Moffitt Cancer Center, Tampa, FL

Background: Circulating tumor DNA (ctDNA) tumor DNA fragments detected in blood sourced from primary malignancy, is an emerging non-invasive tool in oncology for screening, diagnosis, and surveillance. Here, we analyze its utility in patients with metastatic appendiceal neoplasms.

Methods: Following PRISMA guidelines, PubMed, Cochrane, and Clinicaltrials.gov were searched for ‘Appendiceal Neoplasms’ AND Circulating Tumor DNA. Four original studies reporting the role of ctDNA in appendiceal cancer were included after screening 195 articles. The cohort will be split by recent vs. historical ctDNA data for inclusion.

Results: Two studies reported 39% ctDNA positivity rates. Chiang et al. 2023 reported positive ctDNA in 46.2 months and 60 months, respectively, versus not reached for ctDNA negative patients. They frequently presented with liver metastases, which portend a poor prognosis. Singh et al. 2023 reported 50% ctDNA positive rate. Al included patients had KRAS mutation and received hyperthermic intraperitoneal chemotherapy (HIPEC). On 35.6 months follow-up all the patients were alive but one out of two ctDNA positive patients had a relapse at 39 months follow-up.

Conclusions: The use of ctDNA in metastatic appendiceal tumor is not widespread and detection rates are heterogenous. It was observed more in poorly differentiated appendiceal cancers but further studies are needed to evaluate its utility in clinical practice. Research Sponsor: None.
Background: In colorectal cancer (CRC), the use of ctDNA for the purpose of early recurrence detection and prognosis is established, and multiple studies are testing its utility for guiding adjuvant therapy decisions. Tumor informed testing can be performed in clinical situations where adequate tissue is available for next-generation sequencing (NGS). Increasingly, ctDNA testing is being used clinically for colorectal cancer patients and other gastrointestinal (GI) cancers when there is an appropriate clinical scenario and adequate tumor tissue is available for sequencing. Methods: We identified GI cancer patients treated at our institution where SNAGT (Natera) testing was ordered and performed between 2020 – 2023. We included all patients for whom testing was ordered. Then, among patients with any result further analyzed results by disease type, stage, and results. We examined clinical rationale for testing and whether results informed subsequent decisions. Results: A total of 99 GI cancer patients for whom ctDNA testing was ordered were identified. 80 patients had at least 1 ctDNA result including 68 colorectal patients and 12 other GI cancers (anal, bile duct, esophageal, gastric, pancreatic, and small bowel). Among patients with measurable ctDNA, at the most recent testing timepoint 16 had levels that met criteria for positive detection, while 64 were undetectable. Most commonly, testing was ordered in stage III/IV CRC patients for post-operative surveillance. Other clinical use scenarios included 1) surveillance/treatment monitoring in oligometastatic CRC, 2) surveillance in non-metastatic esophageal/gastric cancer, 3) treatment monitoring in MSI-H/immunotherapy sensitive GI cancers. For at least 18 patients, results were a factor in shared clinical decision making between patients and providers. Conclusions: We found ctDNA monitoring is most commonly used in the setting adjusting for CRC patients which is best supported by existing studies. Our data demonstrates that tumor informed testing can be successful in other GI cancers for both surveillance and therapy monitoring. Given the broad and rapid adoption of this technology, there needs to be continued efforts for both prospective validation studies and retrospective real world studies to guide clinical practice. Research Sponsor: None.

Results:

Frequency of BRAF GOF alt types by GI cohort.

<table>
<thead>
<tr>
<th>BRAF Alt Class</th>
<th>Overall</th>
<th>CRC</th>
<th>Non-CRC</th>
<th>p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short variant</td>
<td>2,374 (94%)</td>
<td>1,797 (98%)</td>
<td>577 (80%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Copy number amplification</td>
<td>27 (1%)</td>
<td>0 (0.3%)</td>
<td>21 (3.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fusion</td>
<td>123 (4.9%)</td>
<td>41 (2.2%)</td>
<td>82 (12%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: Meaningful differences were found between the groups in terms of demographics, frequency, and type of BRAF alt and co-occurring mutations. In particular, certain BRAF fusions were present in a higher proportion of other GI cancers and could be an important therapeutic target for this patient population. Research Sponsor: None.
Characterizing the rare abdominal neoplasms of peritoneum, retroperitoneum, and overlapping sites of peritoneum and retroperitoneum: A review of NCT05280847. First Author: Baqir Jafry, UT Southwestern Medical Center, Dallas, TX

Background: The tumor characteristics of the rare abdominal tumors including peritoneum (PT), retroperitoneum (RT) and overlapping sites of peritoneum and retroperitoneum (OT) remain unexplored. Methods: From the National Cancer Database, we identified all patients who were diagnosed with tumors in PT, RT or OT from 2004 to 2016. We evaluated the incidence of each tumor across time and compared population characteristics of each of these tumors. Results: We identified a total of 47300 patients - 20909 had PT; 11837 had RT and 13273 had OT. The mean age of PT was 69.4 years, while that of RT and OT was 61.2 and 68.1 respectively. All three cancers had a higher percentage of females compared to males (93.8% for peritoneum; 50.4% for retroperitoneum; 50.6% for overlapping sites), whites (88.8% for PT; 83.6% for RT; 81.5% for OT), insured patients (97.8% for PT; 96.2% for RT; 96% for OT) and patients without any existing comorbidities (75.9% for PT; 77.5% for RT; 67.7% for OT). The most common histology was adenocarcinoma in PT, leiomyosarcoma in RT, serous epithelial carcinoma among the PT population. These neoplasms had higher proportions of grade 3 tumors (58% for PT; 32% for RT; 50.9% for OT), patients with income $>363.33 (38.6% for PT; 38.1% for RT; 36.6% for OT), and patients residing in an area where 6.3%-10.8% did not graduate from high school (29.8% for PT; 29.7% for RT; 23.8% for OT). From 2004 to 2016, there was a significant increase in the number of tumors of overlapping sites (566 in 2004 to 1484 in 2016) while the number of PT (1580 in 2004 to 1586 in 2016) and RT (726 in 2004 to 980 in 2016) did not change significantly. Conclusions: Among the rare abdominal neoplasms, the number of OT have increased from 2004-2016 while that of PT and RT tumors have remained stable. The histology patterns are consistent with known cancers that involve these regions. Research Sponsor: None.

Evaluating novel therapies and circulating tumor DNA (ctDNA) as a marker of response in curatively treated gastrointestinal cancers with microscopic residual disease. First Author: Reetu Mukherji, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Background: ctDNA has emerged as a novel tool that can identify the earliest sign of relapse (MRD) after curative therapies with specificities of 93-100%, predictive positive values over 98%, and median lead times of 8-9 months before radiographic relapse. ctDNA has allowed us to identify a "new stage" of high-risk patients (pts) with no evidence of disease radiographically (nMRD) and MRD who lack guideline-directed treatment (tx) strategies as, traditionally, they wait for radiographic progression of disease (POD) before starting therapies. Treating MRD is a promising strategy supported by observational studies where ctDNA clearance is linked with improved survival and on-tx ctDNA kinetics predict drug efficacy. We designed a pilot investigator-initiated trial to 1) determine the feasibility of using a surrogate marker, ctDNA, as a rapid signal for positive therapeutic activity and 2) obtain pilot data on the efficacy of a novel combination therapy (atelozculastin [A] + bevacizumab [B]) in eradicating MRD in previously curatively treated pts with Gi cancers. Methods: We will enroll 20 pts with any stage Gi cancers diagnosed within 5 years of curative resection (CRC), n=5 hepatocellular/biliary tract carcinoma, n=5 gastric, n=5 pancreatic adenocarcinoma) who have a positive Signaturect DNA test and nMRD any time after completing standard curative-intent therapies.Pts are treated with A 1200 mg QD + B 15 mg/le/kg IV on day 1 of a 21-day cycle for up to 1 year with imaging every 12 weeks and serial ctDNA testing every 3 weeks. Co-primary endpoints are rates of pt enrollment in 12 months and rates of ctDNA responses at a 12-week landmark after initiation. Pts with ctDNA POD (ctDNA doubling on each of 2 sequential tests, any rate of rise in 3 sequential tests, or radiographic relapse) will stop while those with ctDNA complete response (CR; clearance on 2 sequential tests + ongoing nMRD) or ctDNA partial/stable response (PR; not ctDNA CR or POD + ongoing nMRD) will continuetx. Each cohort's Bayesian predictive probability of positive therapeutic activity will be calculated. If at least 60% of a cohort experiences CR ctDNA, it will be expanded by 5 pts. This scenario is equivalent to Simon’s 2-stage design allowing for a null hypothesis of 20% to 80% alternative hypothesis of at least 60% CR or 5% alpha with 80% power. If at least 5/10 pts in an expanded cohort experience ctDNA CR, this will generate interest in developing a larger confirmatory trial to evaluate pt survival outcomes with A+B and ctDNA as a surrogate for survival. Secondary endpoints are toxicity; reasons for enrollment failure. Exploratory endpoints are associations between ctDNA conversion and disease-free survival, tumor whole exome sequencing data, and peripheral blood immune profiles collected at baseline and on tx. Enrollment began in Q1 2023. 4 pts are enrolled in the CRC cohort. Clinical trial information: NCT05482316. Research Sponsor: Genentech Inc; Natera, Inc.
INSIGHT: A phase 3, randomized, open-label study of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib with KIT exon 11 + 17/18 mutations. First Author: John Raymond Zalcberg, School of Public Health and Preventative Medicine, Monash University, and Alfred Health, Melbourne, Australia

Background: Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal sarcoma with approximately 80% of cases driven by KIT mutations. Most patients (pts) with advanced GIST experience disease progression following first-line treatment with imatinib due to KIT secondary resistance mutations occurring most commonly in the ATP-binding pocket (exons 13/14) and/or activation loop (exons 17/18). Sunitinib is approved as second-line therapy for advanced GIST. Ripretinib is a switch-control tyrosine kinase inhibitor approved for pts with GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib. In the phase 3 INTRIGUE study (NCT03673501) in second-line advanced GIST, ripretinib was not superior to sunitinib in terms of progression-free survival (PFS); however, a more favorable safety profile was observed with ripretinib vs sunitinib. Exploratory mutational analysis from INTRIGUE using baseline circulating tumor DNA (ctDNA) demonstrated that pts harboring primary KIT exon 11 mutations with secondary resistance mutations exclusively in KIT exons 17/18 derived PFS benefit with ripretinib vs sunitinib (median, 14.2 vs 1.5 months; HR, 0.22; 95% CI, 0.11 to 0.44; nominal P < 0.0001). Here, we describe a planned phase 3 study for pts with advanced GIST previously treated with imatinib harboring KIT exon 11 + 17/18 mutations.

Methods: INSIGHT (NCT05734105) is a phase 3, randomized, open-label study aiming to evaluate the efficacy of ripretinib vs sunitinib in pts with advanced GIST previously treated with imatinib and who harbor KIT exon 11 + 17/18 mutations. Eligible pts must be ≥18 years old with histologically confirmed GIST and co-occurring KIT exon 11 + 17/18 mutations confirmed by ctDNA analysis. Pts must also have advanced disease with ≥1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (mRECIST) v1.1, radiologic progression on imatinib, and an Eastern Cooperative Oncology Group performance status ≥2. Key exclusion criteria include a KIT exon 9, 13, or 14 mutation confirmed via ctDNA analysis at screening and prior treatment with another line of therapy in addition to imatinib for advanced GIST. A total of 54 pts will be randomized (2:1) to receive ripretinib 150 mg once daily (QD; continuous) or sunitinib 50 mg QD (4 weeks on/2 weeks off) in 6-week cycles. The primary endpoint is PFS by independent radiologic review (IRR) per mRECIST v1.1; key secondary endpoints are objective response rate by IRR using mRECIST v1.1 and overall survival. Safety and patient-reported outcome measures will also be assessed. Pts randomized to the sunitinib arm may cross over to the ripretinib arm upon disease progression. 1. Bauer S et al. J Clin Oncol. 2022. 2. Bauer S et al. J Clin Oncol. 2023; abstract 397784. Clinical trial information: NCT05734105. Research Sponsor: Deciphera Pharmaceuticals, LLC.