517 General Session

Association of personalized and tumor-informed ctDNA with patient survival outcomes in pancreatic adenocarcinoma.

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Background: Pancreatic adenocarcinoma (PDAC) is the third leading cause of cancer-related death, with a recurrence rate of 85% after curative surgery and a 5-year survival rate of 10%. Serum biomarkers like CA 19-9 lack sensitivity and specificity (10% of patients fail to produce CA 19-9), and are poor indicators of molecular residual disease (MRD). Circulating tumor DNA (ctDNA) detection allows for MRD identification months ahead of radiological findings, and may assess molecular response and patient outcomes. **Methods:** A personalized and tumor-informed multiplex PCR assay (Signatera™ bespoke mPCR NGS assay) was used for the detection and quantification of ctDNA in a prospective clinical cohort of patients. Serial time points were collected for unresectable, borderline resectable, and resectable subsets of patients to monitor ctDNA levels in response to treatment (see Table). **Results:** 93 patients were included, with a median age of 67.3 yrs and 45% female. 285 timepoints were analyzed for ctDNA presence, with each patient having between 1 and 7 timepoints (median 3 timepoints per patient). 46 patients had one or more samples positive for ctDNA, resulting in an anytime ctDNA positivity rate of 49.5%. Anytime positivity correlated with the stage of disease (p<0.001). Within ctDNA-positive samples, observed levels were 0.04-1227 mean tumor molecules per mL of plasma (mean 35.1, median 1.02 MTM/mL). During the follow-up period (median 13.5 months, range 1-80 months), 36 patients had recurrence or disease progression events. Recurrence-free survival (RFS) strongly correlated with post-operative anytime ctDNA positivity: Hazards Ratio 8.0 (95% CI 3.4-18.7), p =1.6e-6. For 49 patients, CA 19-9 measurements were available. Elevated CA 19-9 was not correlated with RFS (p=0.35). **Conclusions:** Our study demonstrates the feasibility of tumor-informed ctDNA-based MRD testing in PDAC, in 93 patients of all stages. ctDNA positivity correlated with patient survival outcomes more strongly than CA19-9. Our data suggests patients can benefit from personalized and tumor-informed MRD testing. Research Sponsor: Natera, Inc.

Cohort characteristics and ctDNA positivity rates.

	Number of patients (N=93)	Patient-level anytime ctDNA positivity	Number of samples (n=285)	Sample-level ctDNA positivity
Overall Pathological Stage I	21 (22.6%)	3/21 (14.3%)	63 (22.1%)	5/63 (7.9%)
Stage II	32 (34.4%)	13/32 (40.6%)	111 (38.9%)	17/111 (15.3%)
Stage III	26 (28.0%)	20/26 (76.9%)	73 (25.6%)	43/73 (58.9%)
Stage IV	14 (15.1%)	10/14 (71.4%)	38 (13.3%)	21/38 (55.3%)
Neoadjuvant Therapy Not Given	51 (54.8%)	24/51 (47.1%)	143 (50.2%)	39/143 (27.3%)
Neoadjuvant Therapy Given	42 (45.2%)	22/42 (52.4%)	142 (49.8%)	47/142 (33.1%)
Resectable Disease	71 (76.3%)	31/71 (43.7%)	219 (76.8%)	53/219 (24.2%)
Unresectable Disease	12 (12.9%)	11/12 (91.7%)	35 (12.3%)	24/35 (68.6%)
Borderline Resectable Disease	10 (10.8%)	4/10 (40.0%)	31 (10.9%)	9/31 (29.0%)

Trybeca-1: A randomized, phase 3 study of eryaspase in combination with chemotherapy versus chemotherapy alone as second-line treatment in patients with advanced pancreatic adenocarcinoma (NCT03665441).

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Background: Eryaspase, asparaginase encapsulated in red blood cells is an investigational product under development. The encapsulated asparaginase induces the degradation of asparagine and glutamine, crucial for cancer cell growth and survival. An earlier Phase 2b study in patients with advanced pancreatic cancer showed an improvement in overall survival (OS) and progression free survival (PFS) with eryaspase plus chemotherapy. **Methods:** TRYbeCA-1 was a randomized, open-label Phase 3 trial of eryaspase combined with chemotherapy in patients with advanced adenocarcinoma of the pancreas who have progressed on only one prior line of systemic anti-cancer therapy. Patients were randomized in a 1:1 ratio to gemcitabine/nab-paclitaxel or irinotecan/fluorouracil (5FU) therapy (depending on first-line received) with or without eryaspase, administered as IV infusion on Day 1 and Day 15 of each 4-week cycle. Key eligibility criteria included progression on or following first-line systemic treatment, ECOG performance status 0 or 1, stage III-IV disease, documented evidence of disease progression, available tumor tissue and adequate organ function. The primary endpoint was OS. A total of 412 events were required for 90% power to detect a treatment effect hazard ratio (HR) of 0.725 at a two-sided significance level of 5%. **Results:** A total of 512 patients were included. Baseline characteristics were well balanced between the treatment arms. The study did not meet the OS primary endpoint [HR: 0.92 (95% confidence interval (CI), 0.76-1.11), p-value 0.375]. The median OS for patients treated with eryaspase plus chemotherapy was 7.5 mo (95% CI, 6.5-8.3), compared to 6.7 mo (95% CI, 5.4-7.5) for chemotherapy alone. There was a trend of nominal OS benefit in 107 patients treated with eryaspase and irinotecan-5FU compared to 109 patients in control subgroup, with a median OS of 8.0 mo versus 5.7 mo, respectively [HR: 0.81 (95% CI: 0.60- 1.09)]. Treatment effect was consistent across various prognosis factors. Median PFS was 3.7 mo vs. 3.5 mo in the eryaspase and control arms, respectively [HR: 0.89 (95% CI: 0.73-1.07), p-value 0.215]. Disease control rate was 57.6% and 49.0% (p-value 0.047) in the eryaspase and control arms, respectively. The most common adverse events were in the eryaspase arm were asthenia, diarrhea, and anemia (Grade 3-4: 16.9%, 7.66% and 17.3%, respectively). Eryaspase did not appear to enhance toxicity of chemotherapy. **Conclusion:** This large prospective study did not meet it primary endpoint of improving OS in patients treated with eryaspase. The addition of eryaspase demonstrated nevertheless a well-tolerated profile and an encouraging survival benefit in the irinotecan/5FU subgroup, warranting further investigation. Clinical trial information: NCT03665441. Research Sponsor: Erytech.

KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRAS^{G12C} mutation.

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Background: KRAS, the most frequently mutated oncogene in cancer, is a key mediator of the RAS/MAPK signaling cascade that promotes cellular growth and proliferation. KRAS mutations occur in approximately 90% of pancreatic cancer, and approximately 2% of these are KRAS^{G12C} mutations. Adagrasib, an investigational agent, is a KRAS^{G12C} inhibitor that irreversibly and selectively binds KRAS^{G12C}, locking it in its inactive state; adagrasib has been optimized for favorable pharmacokinetic (PK) properties, including long half-life (~24 h), extensive tissue distribution, dose-dependent PK, as well as CNS penetration. **Methods:** KRYSTAL-1 (NCT03785249) is a multicohort Phase 1/2 study evaluating adagrasib as monotherapy or in combinations in pts with advanced solid tumors harboring a KRAS^{G12C} mutation. Here we report preliminary data from pts enrolled in a Phase 2 cohort evaluating single-agent adagrasib administered orally at 600 mg BID in previously treated pts with unresectable or metastatic solid tumors (excluding NSCLC and CRC), including pancreatic and other GI cancers. Study endpoints include clinical activity, safety, and PK. **Results:** The data cutoff was 10 September 2021. A total of 42 pts were enrolled in this cohort (median age 63.5 years, range 21–89; 52% female; 71% white; 29%/71% ECOG PS 0/1; median 2 prior lines of therapy, range 1–7; median follow-up 6.3 months), of whom 30 pts had KRAS^{G12C}-mutant GI tumors (12 PDAC, 8 biliary tract, 5 appendiceal, 2 gastro-esophageal junction, 2 small bowel, and 1 esophageal). In a preliminary analysis, 27 pts with GI tumors were evaluable for clinical activity; partial responses (PRs) were seen in 41% (11/27, including 3 unconfirmed PRs); the disease control rate (DCR) was 100% (27/27). Of the 12 pts with PDAC (median 3 prior lines of therapy; median follow-up 8.1 months), 10 were evaluable for clinical activity; PRs were seen in 50% (5/10, including 1 unconfirmed PR); the DCR was 100% (10/10). Median progression-free survival (PFS) was 6.6 months (95% CI 1.0–9.7), and treatment was ongoing in 50% of pts with PDAC. Among the 17 evaluable pts with other GI tumors, 6 achieved PR (35%; 2 unconfirmed) with a DCR of 100% (17/17); 11 pts were still receiving treatment. In the overall cohort, treatment-related adverse events of any grade occurred in 91% (38/42), the most frequent being nausea (48%), diarrhea (43%), vomiting (43%), and fatigue (29%); grade 3/4 events occurred in 21% of pts, with no grade 5 events. **Conclusions:** Adagrasib monotherapy is well tolerated and demonstrates encouraging clinical activity in pretreated pts with PDAC and other GI tumors harboring a KRAS^{G12C} mutation. Further exploration of adagrasib is ongoing in this pt population (NCT03785249). Clinical trial information: NCT03785249. Research Sponsor: Mirati Therapeutics, Inc.

520 **Poster Session**

Race, sex, age, and geographic disparities in pancreatic cancer incidence.

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Background: Pancreatic cancer has a poor prognosis and a 5-year survival rate of 10%. A population-risk level analysis of pancreatic cancer will identify epidemiologic risk factors including geographic, racial, ethnic, and sex inequities which could lead to improved prevention strategies. **Methods:** Incidence data for invasive pancreatic cancer from 2009 through 2018 was obtained from the Surveillance, Epidemiology, and End Results Research (SEER) Plus Limited-Field database (SEER 21) that covers about 37% of the US population. Age-adjusted incidence rates (AAIR) and trends were estimated by race, sex, age categories (ten-year age groups starting from age 30), and county-level rural-urban classification developed by the United States Department of Agriculture (USDA). Trends over the period are described using the annual percent change (APC) calculated using weighted least squares method. **Results:** Overall pancreatic cancer incidence (per 100,000 population) for all ages during 2009-2018 was 13.0. Rates were highest among Black (15.4), followed by non-Hispanic white (13.2) and Hispanic (11.6) groups in both men and women. Males carries a higher rate of incidence (14.8) than females (11.6) in pancreatic cancer although both sexes experienced a 0.6% increase in incidence yearly. Incidence of pancreatic cancer increased with age across all ethnicities in men and women. The highest rate of incidence was found in ages 80 and above (99.5) and the lowest in age group 30-39 (1.0). Pancreatic cancer rates increased by 0.6% yearly and increased in every racial/ethnic group for both males and females, except Black males (0.0) and American Indian/Alaska Native females (-0.2). Although incidence in urban counties (13.1, n = 321) and rural counties (12.8, n = 411) was comparable, rural countries observed a faster increase in rates between 2009 and 2018 (p < 0.05). **Conclusions:** Incidence of pancreatic cancer has increased from 2009 to 2018 across all ethnicities and in both men and women. Minorities, males, and individuals living in rural counties are disproportionately affected by pancreatic cancer. Additionally, older individuals have a higher incidence of pancreatic cancer, suggesting an increased risk in this patient population. This data will inform strategies to identify high-risk populations and implement preventative care, screening, and surveillance. Research Sponsor: None.

Characteristic from 2009-2018	Incidence (per 100,000 population)	95% CI	Trend (APC) [*p < 0.05]	95% CI
Non-Hispanic white	13.2	13-13.3	0.7*	0.6-0.9
Black	15.4	15.2-15.6	0.2	-0.2-0.5
Hispanic	11.6	11.5-11.8	0.5	-0.1-1.1
Asian	10.0	9.8-10.2	0.3	-0.2-0.8
Urban counties	13.1	~	0.6*	0.4-0.7
Rural counties	12.8	~	1.0*	0.6-1.5
Ages 50-59	15.3	15.2-15.5	~	~
Ages 60-69	39.6	39.2-40	~	~
Ages 70-79	72.5	71.8-73.1	~	~
Ages 80 and above	99.5	98.6-100.1	~	~

Association between Environmental Quality Index and metastatic pancreatic cancer.

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Background: Pancreatic cancer ranks as the 3rd leading cause of cancer mortality. Overall more than 50% of patients have metastatic disease at diagnosis. In this study, we evaluated the association between the national level Environmental Quality Index (EQI) and metastatic pancreatic cancer in the US. **Methods:** Adult patients with pancreatic cancer in the SEER database from 2010-2016 were included in this study. The unknown stage was excluded. Patients were categorized into two groups: metastatic vs. non-metastatic disease. EQI provides county-level environmental quality data from 2005-2010 and presents five domains (built, sociodemographic, air, water, land). EQI was categorized into quintiles, with the 5th quantile representing a poorer environmental quality. We used the multivariable logistic regression analysis to assess the association between EQI quintiles and metastatic pancreatic cancer adjusting by age, gender, and race (White, Black, and Others). In addition, the SEER*Stat was used to evaluate the age-adjusted incidence rate, and the correlation coefficient between EQI domains and incidence rate was calculated. **Results:** A total of 75,461 pancreatic cancer patients were included; 55% had metastatic disease. In the adjusted multivariable analysis, metastatic pancreatic cancer was associated with poor built EQI (OR 1.06 [1.01-1.11]). Among metastatic pancreatic cancer patients, poor overall EQI was strongly associated with age > 50 years (OR 1.06 [1.01-1.11]) and Black race (OR 1.29 [1.10-1.51]). Lower built EQI domain was associated with > 50 (OR 1.07 [1.02-1.12]) and White race (OR 1.07 [1.02-1.12]). The incidence rate of metastatic pancreatic cancer was positively correlated with total EQI (rho=0.02, p<0.001), sociodemographic EQI (rho=0.23, p<0.001), land EQI (rho=0.14, p<0.001), and air EQI (rho=0.34, p<0.001). **Conclusions:** Using population-based environmental data, we found built EQI to be associated with metastatic pancreatic cancer. Among metastatic pancreatic cancer patients, total environmental quality was associated with older age at diagnosis and the Black race, while built EQI domain was associated with older age at diagnosis and the White race. Environmental quality was positively correlated with the incidence rate of metastatic pancreatic cancer. Research Sponsor: None.

Multivariable analysis for the association between 5th quintile of EQI total/ domains and metastatic pancreatic cancer.

Factors	Odds	Lower	Upper	p-value
5th EQI Total vs. 1st EQI Total (Ref)	1.045	0.998	1.094	0.059
5th Sociodemographic quintile vs. 1st Sociodemographic quintile (Ref)	1.025	0.981	1.071	0.269
5th Built quintile vs. 1st Built quintile (Ref)	1.057	1.010	1.106	0.018
5th Air quintile vs. 1st Air quintile (Ref)	1.005	0.960	1.053	0.832
5th Land quintile vs. 1st Land quintile (Ref)	1.032	0.987	1.080	0.168
5th Water quintile vs. 1st Water quintile (Ref)	1.047	0.998	1.098	0.060

Poster Session

Liquid biopsy for diagnosis in patients with suspected pancreatic and biliary tract cancers: PREVAIL ctDNA pilot trial.

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Background: Most patients with pancreatic cancer (PC) and biliary tract cancer (BTC) present with advanced disease. In confirmed cases, circulating tumour DNA (ctDNA) may be detected through liquid biopsy in 80-90%. Obtaining a diagnostic biopsy can be technically challenging, require complex invasive procedures and may not be feasible due to comorbidity. Reduction in capacity of aerosol generating diagnostic procedures in many healthcare systems due to COVID19 has highlighted the unmet need for simple, non-invasive diagnostic tools. We piloted the use of ctDNA to support the diagnostic pathway in patients with suspected cancer across 6 tumour types, here we present its use in PC/BTC. **Methods:** This single centre prospective cohort pilot trial was conducted at the Royal Marsden from June 2020 to August 2021. 16 patients were planned each in the PC and BTC cohorts. Eligibility included radiologically suspicious PC/BTC without histological diagnosis, patients with prior non-diagnostic biopsy and inaccessible tumours. Liquid biopsy for ctDNA was collected for plasma based next generation sequencing, using a custom 59 gene panel of common variants in PC/BTC tumours, including analysis for somatic, copy number and structural variants. Clonal haematopoiesis of indeterminate potential (CHIP) and germline variants were identified and subtracted. A molecular tumour board (MTB) reviewed results for interpretation and clinical context. Primary outcome was the proportion of patients with a ctDNA result consistent with a diagnosis of malignancy following MTB discussion. **Results:** 32 patients with suspected PC (n= 16) and BTC (n=16) were recruited. Baseline characteristics are shown in table. ctDNA was detected in 69% and 56% of patients with suspected PC and BTC respectively. MTB discussion confirmed all variants detected were consistent with a diagnosis of malignancy. At the time of data cut off, 23 patients had a subsequent biopsy. The sensitivity and specificity of ctDNA as a diagnostic tool was 80% (90% CI 49.3-96.3) and 100% (90% CI 36.8-100) for PC respectively, and 100% (90% CI 60.7-100) and 75% (90% CI 24.9-98.7) for BTC respectively. There were 2 false negatives in the PC cohort subsequently diagnosed with PC, and 1 false positive in the BTC cohort subsequently diagnosed with oesophageal cancer. **Conclusions:** ctDNA can be used to support a diagnosis of cancer in patients with radiologically suspected PC/BTC. A blood first, tissue second strategy in the diagnosis of PC/BTC could improve diagnostic efficiency, speed, and add resilience to the current diagnostic pathway. Clinical trial information: NCT04566614. Research Sponsor: The Royal Marsden Cancer Charity & NIHR BRC Royal Marsden.

Baseline characteristics.

		PC, n=16 (%)	BTC, n=16 (%)
Age	Median (range)	73 (55-84)	74 (49-90)
Gender	Female	6 (38)	11 (69)
TNM Stage[1]	1	3 (30)	0 (0)
	2	2 (20)	2 (33)
	3	3 (30)	3 (50)
	4	2 (20)	1 (17)
Tumour marker elevation[2]	CEA	7 (58)	1 (9)
	CA19.9	8 (62)	7 (58)

[1] in patients with cancer diagnosed on tissue biopsy. [2] not performed in all patients.

Large scale proteomics of circulating extracellular vesicles to reveal novel biomarkers for pancreatic cancer.

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Background: Robust biomarkers are urgently needed to assist in diagnosing pancreatic cancer. Earlier cancer diagnosis could increase survival rates by an estimated 5-fold and more reliable and real-time assessment of treatment effects in patients with cancer could improve quality of life and reduce healthcare costs. Isolation of circulating extracellular vesicles (cEVs) as 'liquid biopsies' offers an advantageous approach to diagnose and monitor disease status. **Methods:** We conducted a comprehensive proteomics study of cEVs from plasma samples to identify EV proteins that may be used as biomarkers for the diagnosis and prognosis of pancreatic cancer. Patients with pancreatic ductal adenocarcinoma (PDAC) of various tumor stages, chronic pancreatitis, intraductal papillary mucinous neoplasm (IPMN), and age-matched controls were enrolled. EVs were isolated directly from plasma samples using the affinity-based EVTrap method then subject to quantitation by liquid chromatography-tandem mass spectrometry. **Results:** A total of 124 patients (93 with PDAC, 12 with chronic pancreatitis, 8 with IPMN and 11 controls) were included in the discovery cohort. The isolation of EVs with EVtrap allowed the identification on average of 912 EV proteins per 100μL of sample. Principal component analysis of the cEV proteome showed clear separation between PDAC and benign pancreatic diseases. Individuals with IPMN were more closely related to controls, whereas chronic pancreatitis cases were more related to PDAC. At the functional level, we noted that cytokeratin, protein folding chaperons, and actin dynamics regulators were among protein clusters more highly altered in the cEV of patients with PDAC. We further identified new cEV markers associated with metastatic disease, such as PSMB4, RUVBL2, and ANKAR, as well as other EV proteins with strong correlation to prognosis, such as CRP, RALB, and CD55. Finally, we validated a 7-protein PDAC[EV] signature in a validation cohort of 36 separate patients (24 with PDAC, 6 with chronic pancreatitis and 6 with IPMN) which yielded an 89% prediction accuracy for the diagnosis of PDAC. **Conclusions:** This study provides a valuable resource to the scientific community with a comprehensive catalog of novel proteins on circulating EVs that may assist in the development of novel biomarkers and improve the outcomes of patients with pancreatic cancer. Research Sponsor: BIDMC internal seed funding.

524 Poster Session

Development of PCR assays to detect signature circulating tumor DNA methylation markers and KRas mutations for pancreatic ductal adenocarcinoma (PDAC).

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Background: PDAC is a cancer of high mortality. Accurate and cost-effective PCR assays detecting diagnostic and prognostic PDAC markers in blood are desirable for conducting PDAC screening in high-risk populations, evaluating treatments for patients and surveying for post-treatment relapse. **Methods:** We combined PDAC-diagnosing ctDNA methylation markers with PDAC-driving Kras mutations as targets to develop said PCR tests. Methylation markers were previously validated to classify PDAC plasma at a high accuracy by a targeted methylation sequencing assay. Seven known PDAC driver mutations in KRas exon2 were selected. Taqman-based quantitative methylation-specific PCR (MSP) and ARMS PCR were designed for methylation markers and KRas mutations, respectively, and were validated for technical performances. A step of pre-amplification of input DNA by conventional PCR was included prior to quantitative PCR to improve sensitivity. Over 200 clinical PDAC and control tissue and plasma samples were used to determine their analytical performances in classifying PDAC plasma. **Results:** All targets were detected at a limit-of-detection of 0.25% or better on standards DNA in PCR. To test clinical plasma samples, methylation markers were first filtered by comparing their levels in PDAC-, para-tumor tissues and whole blood cells. Twenty-four most discriminatory markers for PDAC tissues were selected and used to classify 110 PDAC plasma samples from equal number of normal samples. They were evaluated for their sensitivity at a pre-set specificity of 90%. The 4 best-performing markers were selected to build and cross-validate a general-linear-model (GLM) PDAC classifier, which achieved a sensitivity of 66% at 90% specificity (AUC = 0.829) in cross-validation. Adding status of KRas mutations further improved prediction accuracy by increasing sensitivity to 75% (AUC = 0.89), demonstrating the methylation markers and KRas mutations complement each other in detection PDAC plasma. **Conclusions:** Our results suggest that a small number of our DNA methylation markers can classify PDAC plasma at a reasonably high accuracy by MSP. Incorporating KRas driver mutations further improved classification accuracy. Together they are promising to be further translated into diagnostics for PDAC early screening, treatment assessment and postoperative surveillance. Research Sponsor: None.

525 Poster Session

Hypofractionated radiotherapy to the pancreas: U.K. experience.

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Background: During the COVID19 pandemic, many centres in the UK, shifted towards utilising hypofractionated radiotherapy (RT) to pancreas. We aim to report the UK experience in hypofractionated radiotherapy to the pancreas in 2020. **Methods:** We retrospectively identified patients receiving either moderate hypofractionated (15 fractions) or ultra-hypofractionated (3-5 fractions) RT to the pancreas from 7 centres in the UK. Rates of toxicity, progression, death and potential prognostic factors were assessed. Univariate and multivariate Cox proportional hazards analyses were performed. **Results:** 92 patients from 7 centres were included in the analysis (median age 71 (range 49-88). 90% had performance status of 0-1. 66% had locally advanced disease. 53% had RT delivered over 3-5 fractions (n = 49, median: 30Gy/5f, range:30-40Gy in 3-5f). The rest had 15-fraction RT with or without concurrent chemotherapy (n = 43, median: 45Gy/15f, range: 36-45Gy/15f). Induction chemotherapy (CT) was used in 64% (FOLFIRINIOX –42/59). Median follow-up was 13 months from first treatment (induction CT or RT). Median overall survival (OS) among all patient was 17 months, (95% CI-14.5-19.5 months). On multivariable analysis, induction CT was the only predictor of improved PFS (median survival (MS) 12 vs 5 months; hazard ratio [HR] 0.23; 95% confidence interval [CI]: 0.12-0.44, p < 0.001) and OS (MS 24 vs 11 months; HR 0.15; 95% CI: 0.07 – 0.34, p < 0.001). There were no deaths. 4 patients had grade 3+ toxicities (transaminitis, cholecystitis and gall bladder perforation, small bowel obstruction and diarrhoea) –all had concurrent CT. **Conclusions:** Our survival outcome appears to be comparable with published data from CT + concurrent chemoradiotherapy. Induction CT appears to improve outcome. Careful selection of patients can help maximise advantage in this patient population. Research Sponsor: None.

526   **Poster Session**

A multi-institutional study of the impact of the COVID-19 pandemic on pancreatic cancer diagnosis and management.

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Background: The impact of COVID-19 on cancer patients may be attributed not only to its direct effects on the immune system but also to delays in diagnosis and treatment. Data on the effects of COVID-19 on pancreatic ductal adenocarcinoma (PDAC) patients are scarce. Therefore, we set out to determine the impact of the pandemic on diagnosis and treatment initiation. We hypothesized that time from diagnosis to treatment would be increased in the COVID era compared to the pre-COVID era. **Methods:** We conducted an IRB-approved retrospective chart review of 488 patients diagnosed with PDAC from March 2019 to September 2020 at two academic medical centers. Patients were divided into two groups, based on the date of initial pathologic diagnosis. We defined the pre-COVID era as March 2019 to March 2020, the 12-month time period before California's statewide lockdown. The COVID era was defined as the 6 months following the lockdown, March 2020 to September 2020. Demographics, clinical stage, and treatment type were recorded. In addition, initial clinical encounter date, pathologic diagnosis date, and initial treatment date were also collected. All data were gathered at two large-scale academic institutions. Descriptive statistics were used in the analysis. **Results:** There were 333 patients diagnosed during the pre-COVID era and 155 patients during the COVID era. While race/ethnicity and age at diagnosis were statistically similar for both groups, females made up a significantly larger proportion of COVID era patients than pre-COVID era patients ($p = 0.02$). There was no significant difference in clinical stage at diagnosis between the two groups ($p = 0.84$). In the pre-COVID era, 19.5% of cases were resectable, 11.1% borderline resectable, 20.1% locally advanced, and 31.8% metastatic. In the COVID era, 17.4% of patients were resectable, 11% borderline resectable, 23.9% locally advanced, and 32.9% metastatic. Median time from pathologic diagnosis to initiation of treatment was 32 days for the pre-COVID era patients and 28 days for the COVID era patients ($p = 0.38$). Initial treatment type was also similar between the two groups ($p = 0.29$). **Conclusions:** Fortunately, our data indicate that the COVID-19 pandemic has not significantly prevented PDAC patients from seeking care. Additionally, it does not appear that COVID-19 has delayed treatment initiation or changed initial treatment type. We believe that the successful adoption of telemedicine and other safety protocols have allowed patients with PDAC to continue receiving appropriate care during the pandemic. Research Sponsor: University of California, Irvine.

Impact of California COVID-19 lockdown on diagnosis and median time to treatment (days).

	Pre-COVID Era (Days, 95% CI)	COVID Era (Days, 95% CI)	p-value
Time from symptom onset to clinical encounter	21 (14-31)	21 (15-31)	0.65
Time from clinical encounter to diagnosis	11 (9-13)	13 (10-17)	0.15
Time from diagnosis to treatment	32 (26-36)	28 (25-32)	0.38

Cancer Commons' virtual tumor board program: A patient-centric advisory panel and real-world data registry.

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Background: We initiated a nationwide Virtual Tumor Board (VTB) program for pancreatic cancer (PC) patients (pts). The VTB consists of oncology experts and serves as an advisory panel by providing information on treatment (Tx) options based on a comprehensive review of patients' oncologic history. Personalized Tx options and their rationales are provided and outcomes tracked in a prospective registry (XCELSIOR). **Methods:** PC pts who participated in XCELSIOR shared access to their full medical records, which were collected, processed, and abstracted. The panel reviewed cases asynchronously through an interactive platform followed by a VTB which was held weekly through videoconferencing. Tx options were summarized into a written report and provided to patients and their physicians. Outcomes and quality of life are tracked longitudinally through an IRB-approved 21CFR11 compliant observational registry (XCELSIOR). **Results:** From 9/2020 to 8/2021, the VTB reviewed 79 unique cases; 56% were male; median age at diagnosis was 66 (50-87). At the time of VTB, 68 (87%) had metastatic disease and 8 (10%) had locally advanced disease. Median prior therapy lines was 2 (0-9), with 26 (35%), 24 (32%), 6 (8%), and 19 (25%) pts having received 1, 2, 3 and 4+ lines of therapy, respectively. Median time from diagnosis for pts presenting after 1, 2, and 3+ lines of prior Tx was 9.5, 11, and 17.5 months, respectively. First-line Tx was FOLFIRINOX in 40 (53%) pts and gemcitabine/nab-paclitaxel in 22 (29%) pts. At the time of VTB, 32 (37%) of patients had stable disease, 23 (26%) had disease progression, 18 (21%) had recently started a new Tx, 7 (8%) were responding to Tx, 3 (3%) had stable disease on imaging but rising CA 19-9, and 4 (4%) were others. Prior to VTB, 69 (87%) pts had molecular profiling results available. Collectively the VTB provided 375 Tx and diagnostic (NGS, imaging, etc.) options with a median of 4 (1-12) options per patient. As of 9/8/2021, 87 VTB reports were provided. Of 25 instances of 'no Tx decision', 10 (40%) are deceased, 10 (40%) are stable, and 5 (10%) had other reasons. Of the 25 people who started a subsequent Tx, 14 (56%) were identified by the VTB. These included 9 (64%) FDA-approved, 3 (21%) off-label, and 2 (14%) on-trial Tx. Tx not identified by the VTB included 3 (33%) FDA-approved, 2 (22%) off-label, 2 (22%) on-trial, and 2 (22%) local Tx. **Conclusions:** We present our experience of utilizing a platform for patients to receive a virtual tumor board review and utilize an IRB-approved registry as a learning system. Early data indicate successes in identifying treatment and clinical trial opportunities. Future steps include streamlining communication with primary oncologists and enhancing access to treatments. NCT03793088. Research Sponsor: Cancer Commons.

Feasibility and utility of synthetic control arms derived from real-world data to support clinical development.

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Background: 'Synthetic' control arms (SCAs), created using electronic health records (EHRs), have immense potential to augment clinical trial findings and provide a rich context of real-world evidence (RWE) while reducing patient (pt) and sponsor burden (Gottlieb 2019). PICI0002 (PRINCE) is a ph1b/2 study evaluating APX005M with gemcitabine (gem) and nab-paclitaxel (NP) ± nivolumab for the treatment of metastatic pancreatic adenocarcinoma (mPDAC; NCT03214250). PRINCE pts were enrolled from select US academic cancer centers and a global, ph3 study was utilized for an historical reference control (Von Hoff 2013). To address the perceived limitations of this design, we explored the feasibility and utility of developing a contemporary SCA using real-world data (RWD). **Methods:** The SCA was derived using retrospective pt data from the two highest enrolling participating centers on PRINCE. Pts meeting key PRINCE eligibility criteria, who received gem/NP in the two years preceding the trial start date, were identified using an electronic phenotyping algorithm applied to cancer registry and EHR data, followed by manual review. Baseline characteristics, treatment exposure, efficacy and survival data were extracted electronically and via manual chart abstraction. Data were stored in a REDCap database built and housed by the Parker Institute for Cancer Immunotherapy. SCA pt characteristics were compared with PRINCE and overall survival (OS; time from initiation of gem/NP to death) was compared to historical reference controls (Table). **Results:** N=68 pts treated with gem/NP meeting PRINCE eligibility criteria were identified. All pts were deceased at the time of analysis. SCA pts had comparable baseline characteristics to PRINCE pts; key differences included inferior performance status and a higher proportion of pts presenting with a de novo mPDAC diagnosis. Median time on gem/NP was 4.8 months (mos; range 0-39). Median OS was 11.5 mos (95% CI 9.0-13.6) and 1-year OS was 43% (95% CI 31-55), in line with historical controls (Table). **Conclusions:** This study confirms the feasibility and utility of generating a control arm via a semi-automated approach. Current limitations entail manual oversight requirements as well as the known constraints of RWD, including associated biases and lack of available RECIST data. These limitations stand to evolve alongside EHR technologies. SCAs using RWD may help inform the value of prospective data by providing a contemporary reference of RWE. In some circumstances, SCAs may also serve as an alternative to traditional control arms, particularly for well-characterized standard therapies. Research Sponsor: None.

Trial (Year)	N	Median OS (mos; 95% CI)	1-yr OS Rate (%; 95% CI)
SCA	68	11.5 (9.0-13.6)	43 (31-55)
Tempero (2021)	213	10.8 (NR)	43* (NR)
Van Cutsem (2020)	165	11.5 (9.0-12.5)	45* (NR)
Von Hoff (2013)	431	8.5 (7.9-9.5)	35 (30-39)

*Manually estimated from Kaplan-Meier curve; NR = Not reported.

529 Poster Session

Real-world cost-effectiveness of first-line gemcitabine + nab-paclitaxel versus FOLFIRINOX in patients with advanced pancreatic cancer: A population-based retrospective cohort study in Ontario, Canada.

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Background: Currently, there are no direct randomized control trials (RCTs) comparing gemcitabine and nab-paclitaxel (Gem-Nab) and FOLFIRINOX for advanced pancreatic cancer (APC). Thus, previous model-based cost-effectiveness analyses were based on indirect comparisons of RCT data. While it is well known that RCT-based efficacy does not often translate to real-world effectiveness, there is limited literature investigating the comparative cost-effectiveness of Gem-Nab versus FOLFIRINOX for APC in the real-world. The objective of this study is to examine the real-world cost-effectiveness of Gem-Nab versus FOLFIRINOX in patients with APC in Ontario, Canada. **Methods:** This population-based retrospective cohort study compared all patients treated with first-line Gem-Nab or FOLFIRINOX for APC with ECOG performance status 0-1 in Ontario from April 2015 to March 2019. Patients were linked to administrative databases to identify key characteristics and costing data. Using propensity scores and a stabilizing weights method, an inverse probability of treatment weighted cohort was developed. Mean survival and total costs were calculated over a 5-year time horizon, adjusted for censoring and discounted at 1.5% (per Canadian guidelines). Incremental cost-effectiveness ratio and net monetary benefit were computed (measured in life-years and quality-adjusted life years) to estimate cost-effectiveness from the public healthcare payer's perspective. A sensitivity analysis was conducted using the propensity score matching method. **Results:** 1,988 patients were identified (Gem-Nab: 928, FOLFIRINOX: 1,060). Mean survival was lower for patients in the Gem-Nab group than the FOLFIRINOX group (0.98 versus 1.26 life-years, incremental -0.28 (95% confidence interval -0.47, -0.13)). Patients in the Gem-Nab group also incurred greater mean 5-year total costs (Gem-Nab: $103,884, FOLFIRINOX: $101,518). Key cost contributors include ambulatory cancer care, acute in-patient hospitalization, and systemic therapy drug acquisition. Gem-Nab was dominated by FOLFIRINOX, as it is less effective and more costly. Results from the sensitivity analysis were similar. **Conclusions:** In routinely treated unselected patients, Gem-Nab is likely more costly and less effective than FOLFIRINOX and therefore, not considered cost-effective at any commonly accepted willingness-to-pay threshold. Research Sponsor: The Canadian Centre for Applied Research in Cancer Control (ARCC) is funded by the Canadian Cancer Society Research Institute grant #2015-703549.

530   **Poster Session**

Optimal preoperative multidisciplinary treatment in borderline resectable pancreatic cancer: Results of a dual-center study.

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Background: For borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC), upfront surgery was standard in the past, and the usefulness of neoadjuvant treatment (NAT) has been reported in recent years. However, few studies have been conducted to date on whether there is a difference in optimal treatment between BR-PDAC invading the portal vein (BR-PV) or abutting major arteries (BR-A). The objective of this study was to investigate the optimal treatment for BR-PV and BR-A. **Methods:** We retrospectively analyzed 199 patients with BR-PDAC (88 BR-PV and 111 BR-A). For each BR-PV and BR-A, we analyzed the following points. 1) Comparison of prognosis of upfront surgery vs. NAT, 2) Comparison of regimens in patients who underwent NAT, 3) Prognostic factors in patients who underwent resection after NAT. **Results:** 1) In BR-PV patients who underwent upfront surgery (n = 46)/NAT (n = 42), survival was significantly better in the NAT group (3-year overall survival (OS): 5.8%/35.5%, $p = 0.004$). In BR-A patients who underwent upfront surgery (n = 48)/NAT (n = 63), survival was also significantly better in the NAT group (3-year OS:15.5%/41.7%, $p < 0.001$). 2) The prognosis tended to be better in patients who received newer chemotherapeutic regimens, such as FOLFIRINOX and gemcitabine with nab-paclitaxel than older regimens such as gemcitabine and/or S-1, in each BR-PV and BR-A patients. The R0 rate was significantly higher (100%) when radiotherapy was used in combination with chemotherapy, regardless of the chemotherapeutic regimen. 3) In 36 BR-PV patients who underwent surgery after NAT, univariate analysis revealed that normalization of tumor marker levels ($p = 0.028$) and preoperative high prognostic nutritional index (PNI) ($p = 0.022$) were significantly associated with a favorable prognosis. In 39 BR-A patients who underwent surgery after NAT, multivariate analysis revealed that preoperative PNI > 42.5 was an independent prognostic factor (hazard ratio: 0.15, $p = 0.014$). The length of NAT was not a prognostic factor for either BR-PV or BR-A. **Conclusions:** NAT using newer chemotherapy is essential for improving the prognosis of BR pancreatic cancer. These findings suggest that prognosis may be improved by maintaining good nutritional status during preoperative treatment, not by the length of preoperative treatment. In addition, surgery after normalization of tumor markers levels by preoperative treatment contributes to the prolongation of survival. Research Sponsor: None.

531   **Poster Session**

Resource utilization and total cost of care among Medicare advantage patients with metastatic pancreatic cancer receiving NCCN category 1 preferred regimens.

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Background: Medicare Advantage accounts for almost 40% of Medicare beneficiaries in 2021. There is limited research evaluating utilization and cost for Medicare Advantage patients with metastatic pancreatic cancer (m-PANC) receiving various NCCN Category 1 preferred regimens. **Methods:** We used ICD-10 diagnosis codes to identify patients with m-PANC without end-stage renal disease in the 2016-2019 Milliman Consolidated Health Cost Guidelines Sources Database (CHSD) claims files. Study patients had 2+ claims with a pancreatic cancer diagnosis and Medicare Advantage coverage for 3 months pre- and 1 month post-metastasis diagnosis. Patients with stand-alone Part D plan coverage or aged<65 years were excluded. Total cost of care (TCOC) was the sum of the average paid by the insurer and patient. Study patients were treated with NCCN Category 1 preferred regimens: 1L gemcitabine/nab-paclitaxel (gem/nab), 1L gemcitabine monotherapy (gem mono), 1L FOLFIRINOX (FFX), and 2L+ liposomal irinotecan (5FU was not included in this analysis; see Limitations for further details). **Results:** Of the approximately 2.5 million patients covered by Medicare Advantage in CHSD, there were 946 patients that received an NCCN Category 1 chemotherapy regimen between 2016 and 2019. Among NCCN Category 1 preferred regimens, patients receiving 2L+ liposomal irinotecan had the lowest mean admissions per beneficiary and mean readmission rate (0.5 and 8%) compared to patients receiving gem/nab (0.8 and 12%), gem mono (0.6 and 8%), or FFX (0.6 and 9%). Patients receiving 2L+ liposomal irinotecan also had the shortest length of stay per inpatient admission in days (2.9) compared to patients receiving gem/nab (5.1), gem mono (3.6), or FFX (4.3). Mean claims per beneficiary for emergency department observations was lowest among patients receiving 2L+ liposomal irinotecan (0.7), compared to patients receiving gem/nab (0.9), gem mono (1.0), or FFX (0.89). Patients receiving 2L+ liposomal irinotecan had lower median TCOC ($31,885) than patients receiving gem/nab ($39,479) or FFX ($32,632). **Conclusions:** Patients with Medicare Advantage receiving 2L+ liposomal irinotecan-based regimens to treat m-PANC had lower healthcare resource utilization in key categories and lower median total costs than patients receiving other NCCN Category 1 preferred regimens. Limitations: Analysis of different populations or time periods may yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance might influence which regimens patients receive. We did not adjust TCOC or utilization for LOT durations. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5FU or prior gemcitabine-based therapy. Research Sponsor: Ipsen Biopharmaceuticals Inc.

532   **Poster Session**

Real-world clinical outcomes and molecular features of lung-specific and liver-specific metastases in pancreatic ductal adenocarcinoma (PDAC).

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Background: PDAC remains one of the most lethal malignancies following metastatic presentation, typically to the liver or lung. Previous studies have observed that advanced PDAC patients have variable outcomes depending on site of involvement. Here, we aim to understand survival outcomes and molecular features for PDAC based on involvement of lung vs liver. **Methods:** We retrospectively analyzed longitudinal clinical outcomes across 787 patients with PDAC with next generation sequencing (NGS) from Perthera's Real-World Evidence database whose tumors first metastasized to either the lung or the liver. Median overall survival (mOS) was measured from either the date of initial diagnosis (resectable cases only, stage I-III) or advanced diagnosis (stage IV) until death. Differences in survival and frequencies of mutations were evaluated between patients with lung-specific and liver-specific metastases using Cox regression and Fisher's exact test, respectively. **Results:** Among resectable PDAC, mOS from initial diagnosis was significantly shorter in patients that developed liver only metastasis (Table, left) compared to those patients that developed lung only metastasis (p=2.4e-08, HR=3.04 [2.06-4.49]). In the advanced PDAC cohort, mOS from diagnosis of advanced disease was also significantly shorter (Table, right) in liver only versus lung only metastasis (p=0.0013, HR=1.62 [1.21-2.18]). Differences in treatment-specific outcomes were not significant supporting a potential prognostic role for lung only metastases. PDAC tumors presenting to the liver first were modestly enriched (unadjusted p<0.05) for TP53 mutations (81.4% in liver vs 69.2% in lung), MYC amplifications (8.6% vs 3.0%), and inactivating CDK2NA alterations (51.5% vs 39.1%) whereas lung-specific mutation frequencies were higher for STK11 mutations (2.4% in liver vs 7.5% in lung), CCND1 amplifications (0.5% vs 3.0%), GNAS alterations (2.0% vs 8.5%). No differences in KRAS mutations nor specific isoforms were noted between lung vs liver only metastasis. **Conclusions:** Lung only metastasis in both resectable and advanced PDAC confers a significant survival advantage compared to liver only metastasis. Deeper investigation into the molecular drivers of site-specific metastases is warranted. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Real-world overall survival outcomes in PDAC tumors that first metastasized to either the lung only or the liver only.

Group	Resectable PDAC Cohort		Advanced PDAC Cohort	
	# Patients	mOS [95% CI]	# Patients	mOS [95% CI]
Liver only metastases	170	2.3y [1.9-2.8]	485	1.3y [1.2-1.5]
Lung only metastases	95	5.1y [3.9-7.3]	102	2.0y [1.8-2.5]

533 **Poster Session**

Early-onset pancreatic cancer: Defining contemporary presentation, treatment, and outcomes in the under 50 age group using real-world data.

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Background: The incidence of pancreatic cancer is increasing in younger patients (pts). Early onset pancreatic cancer (EOPC) is reportedly diagnosed at a later stage, potentially compromising outcomes compared to later onset pts (LOPC). With recent gains in staging and neo/adjuvant regimens, we sought to elaborate on the characteristics of EOPC and LOPC in a contemporary real-world cohort. **Methods:** The PURPLE registry, a prospectively collected multi-site data set on consecutive pancreatic cancer pts was interrogated. Patient, tumor, treatment and outcome data were extracted for EOPC vs LOPC. EOPC were those diagnosed prior to age 50 and LOPC after age 50. Resectability status was per MDT consensus. **Results:** Of 1534 pts, 93 (6%) were EOPC (51% male) and 1442 (94%) LOPC (51% male). EOPC had better ECOG performance status (0-1: 95% vs 81%, Relative Risk [RR] 1.2, p < 0.001) and Charlson Comorbidity Index Score (0-2: 98% vs 28%, RR 3.5, p < 0.001). Primary tumor site (head/body/tail: 66%/11%/20% for EOPC and 68%/17%/14% for LOPC), and staging (resectable/borderline resectable/locally advanced/metastatic: 29%/16%/14%/41% for EOPC vs 28%/9%/21%/41% for LOPC) did not differ. 25 (93%) of EOPC and 320 (79%) LOPC resectable pts underwent resection (p = 0.13). 12 (80%) EOPC and 36 (26%) LOPC borderline resectable pts underwent resection (RR 3.0, p < 0.001). Resection margin status (R0 vs R1 vs R2) did not differ. Resected EOPC more frequently received neoadjuvant therapy (30% vs 9%, RR 3.2, p = 0.001). EOPC were more likely to receive palliative chemotherapy in the advanced/metastatic setting (77% vs 49%, RR 1.6, p < 0.001), and were more likely to receive first line (1L) FOLFIRINOX than gemcitabine-nab-paclitaxel (36% vs 18%, RR 2, p = 0.019). Median overall survival (OS) was superior for EOPC (24 vs 12 months, Hazard Ratio [HR] 0.55, p < 0.001). For resectable pts, relapse free survival (RFS) did not differ but OS was superior for EOPC (undefined vs 27.7 months, HR 0.26, p = 0.004). In borderline resectable pts, RFS was similar and OS only numerically superior for EOPC (31.2 vs 17.7 months, p = 0.20). For locally advanced disease, 1L progression free survival (PFS1) was similar and OS was superior for EOPC (27.8 vs 11 months, HR 0.40, p = 0.008). There was no difference in PFS1/OS for metastatic pts. **Conclusions:** EOPC are fitter, with similar stage at diagnosis as LOPC. EOPC are more likely to receive neoadjuvant chemotherapy and undergo resection when presenting with borderline resectable disease. EOPC receive more treatment and have superior OS, with RFS/PFS1 not statistically different to LOPC. Research Sponsor: None.

534 **Poster Session**

Patient-reported outcomes (PROs) in pancreatic cancer clinical trials (CTs).

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Background: Incorporating PROs into CTs is critical for patients with pancreatic cancer, as these individuals often experience a high symptom burden and prioritize maximizing quality of life (QOL). **Methods:** We reviewed protocols of completed U.S. CTs listed on ClinicalTrials.gov that investigated curative/palliative interventions in pancreatic cancer from 1995-2020. We assessed up to August 2021 if CT publications reported PRO results through linked publications and an independent search through PubMed/MEDLINE. We extracted CT details (funding, eligibility, etc), and if PROs (outcome directly reported by patients) were listed as an endpoint (primary/secondary/exploratory). We classified interventions as cancer-directed (e.g. chemotherapy), supportive care (e.g. neurolysis), or other (e.g. curcumin). **Results:** We reviewed 619 protocols and included 379 in the analysis. Most CTs investigated cancer-directed interventions (317, 83.6%). Only 43 (11.4%) included PROs as endpoints (Table). In these, most of the PROs assessed QOL (34, 79.1%) and pain (15, 34.9%). For the 33/43 (76.7%) protocols that listed a specific PRO instrument, EORTC-QLQ C30 (11/33, 33.3%) was the most common. Only 6 (18.2%) protocols included pancreatic cancer-specific PROs, such as QLQ-PAN26. Supportive care CTs were more likely to assess PROs than cancer-directed CTs (odds ratio, OR= 62.6, 95% CI 16.7-234.3, p<0.0001). Protocols listed PROs as a primary, secondary, and exploratory endpoint in 15 (34.9%), 25 (58.1%), and 3 (6.9%) CTs respectively. Most CTs (13/15, 86.7%) with PROs as a primary endpoint evaluated supportive care interventions. Of 15 CTs with PROs as a primary endpoint, 10 (66.7%) had results published. Of 28 CTs assessing PROs as a secondary/exploratory outcome, 20 (71.4%) had published results and 12 (42.9%) included PRO data. **Conclusions:** From 1995-2020, only 11.4% of pancreatic cancer CTs incorporated PROs as endpoints. Supportive care CTs were more likely to include PROs than cancer-directed CTs. Our findings underscore the need to improve efforts to incorporate PROs into CTs for patients with pancreatic cancer. Data as number (%). Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Characteristics.

		Total CTs (N=379)	Assessing PROs of total eligible CTs (N=43 of 379)	p-value
CT commencement year	1995-2000	21 (5.5)	1/21 (4.8)	
	2001-2005	91 (24.0)	10/91 (11.0)	
	2006-2010	108 (28.5)	10/108 (9.3)	
	2011-2015	113 (29.8)	14/113 (12.4)	0.64
	2016-2020	46 (12.1)	8/46 (17.4)	
Intervention	Cancer-directed	317 (83.6)	22/317 (6.9)	
	Supportive care	17 (4.5)	14/17 (82.4)	<0.0001
	Other	45 (11.9)	7/45 (15.6)	
Funding	Academic	84 (22.1)	15/84 (17.9)	
	Corporate	138 (36.4)	14/138 (10.1)	0.04
	Academic/NCI	88 (23.2)	6/88 (6.8)	
	Other	64 (16.9)	7/64 (10.9)	
Stage	Unresectable	320 (84.4)	29/320 (9.1)	
	Resectable	42 (11.1)	9/42 (21.4)	0.02
	Any	17 (4.5)	5/17 (29.4)	

535   **Poster Session**

Impact of venous thromboembolism in hospitalized patients with pancreatic cancer: A nationwide inpatient sample (NIS) study.

Nishanth Thalambedu, Waqas Ullah, Sravani Gundarlapalli; UAMS Myeloma Center, Little Rock, AR; Thomas Jefferson University Hospital, Philadelphia, PA

Background: Pancreatic cancer (PC) has a strong association with venous thromboembolism (VTE) but the impact of it on mortality and morbidity is unknown. Inpatient costs contribute significantly to the overall cancer care costs even though there is a modest improvement in survival of pancreatic cancer patients. This study aims to determine the mortality trends and associated health care utilization in PC patients with and without VTE and to analyze its impact on hospitalized patients. **Methods:** We used National Inpatient Sample (NIS) to extract data for all patients above 18years of age hospitalized with a primary diagnosis of Pancreatic cancer from 2002-2018 using ICD-9 and ICD-10 codes. Unadjusted odds ratio for dichotomous outcomes were calculated, and independent t test analysis was done for continuous outcomes. **Results:** The odds of all-cause mortality (OR 1.35, 95% CI 1.33-1.37, $p<0.001$) and stroke (OR 1.82, 95% CI, 1.76-1.87, $p<0.001$) were significantly higher in pancreatic cancer patients with VTE compared to without VTE. PC patients with VTE were found to have significantly higher average cost of hospitalization (US \$56101 vs US \$46325, $p<0.001$) and longer length of stay(LOS) (8.20 vs 6.83, $p<0.001$) when compared to patients without VTE. **Conclusions:** Hospitalized PC patients with VTE have higher odds of mortality and stroke when compared to PC patients without VTE. Similarly, VTE in PC patients is shown to increase the hospitalization costs and overall length of stay. Research Sponsor: None.

In-Hospital outcomes of all patients with pancreatic cancer without VTE and with VTE. Comparison of in-patient outcomes of continuous variables on Mann-Whitney U test analysis.

Variable	No VTE	VTE	uOR (95% CI)	p=value
Mortality	186199 (9.1%)	20439 (11.8%)	1.35 (1.33-1.37)	<0.0001
Stroke	34628 (1.7%)	5216 (3%)	1.82 (1.76-1.87)	<0.0001

Continuous Variables	No VTE (2058088)	VTE(173028)	P-value
Length of stay	6.83 ± 6.997	8.20 ± 8.391	<0.0001
Total charges	46325.59 ± 66711.056	56101.0± 85275.526	<0.0001

536   **Poster Session**

Cost-effectiveness of universal screening for germline BRCA mutations in metastatic pancreatic cancer.

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Background: Germline *BRCA*1/2 mutations (gBRCAm) increase the risk of pancreatic ductal adenocarcinoma (PDAC). The NCCN 2020 guidelines recommend testing for gBRCAm in metastatic PDAC patients if the patients have a personal history and/or familial history of PDAC (current standard-of-care). However, given the advances made in genetic testing, universal gBRCAm testing for metastatic PDAC patients can be considered. The cost-effectiveness of universal gBRCAm screening has yet to be compared to the current standard-of-care. The purpose of our study was to explore the cost-effectiveness, treatment outcomes, costs, and quality-of-life impact of universal gBRCAm screening. **Methods:** We developed a decision-analytic mathematical model comparing the cost and health outcomes of universal gBRCAm screening against the current standard-of-care. Inputs for the model were estimated using clinical trial data and published literature. No intervention was used as a comparator. The primary endpoint was incremental cost-effectiveness ratios (ICERs) with a willingness-to-pay (WTP) threshold of $100,000 per quality-adjusted-life-year (QALY). Secondary endpoints included overall survival (OS), progression-free survival (PFS), life-years (LYs) and total cost of care (USD). **Results:** Universal gBRCAm screening was the cost-effective strategy, totaling incremental QALYs of 1.61 at a cost of $73,682 per QALY when compared to no intervention. A one-way sensitivity analysis found that the standard-of-care becomes the cost-effective strategy when the prevalence of gBRCAm is lowered to 2% of the base case. **Conclusions:** Our model found that universal gBRCAm screening is cost-effective and even cost-savings for patients with metastatic PDAC. Additional clinical trial data with sufficient follow-up are needed to confirm our findings. Research Sponsor: U.S. National Institutes of Health.

Model results.

	Life Years	Cost (USD)	QALYs	BRCA Status (%)	Median OS/ PFS	5 Year OS/ PFS	ICERs
No Intervention	0.856	$131,382	0.377	N/A	9.73/4.94	0/0	–
Universal gBRCAm Screening	1.61	$190,358	1.18	7%	17.21/9.24	1.20%/ 1.08%	$73,682
Standard-of-Care	1.60	$191,702	1.17	1.4%	17.06/9.22	1.12%/ 1.03%	Dominated

Health outcomes of gBRCA testing strategies for metastatic pancreatic cancer patients.

Lin Fan, Neeharika Agnihotri, Apoorva Ambavane, Weiyan Li, Seongjung Joo, Hyun Kyoo Yoo, Dominic Muston; Merck & Co, Inc., kenilworth, NJ; Evidera, London, United Kingdom; Evidera, London, MD, United Kingdom; AstraZeneca, Gaithersburg, MD; Merck & Co., Inc., Kenilworth, NJ; AstraZeneca, Cambridge, United Kingdom; Merck.Inc, Kenilworth, NJ

Background: About 4-8% metastatic pancreatic cancer (mPC) patients have germline BRCA mutation (gBRCAm). Identifying gBRCAm through early testing benefits mPC patients through: 1. better health outcomes when gBRCAm patients receive platinum (plat) based 1st line (1L) chemotherapy compared to non-plat 1L regimen; 2. additional benefit, if eligible, from olaparib (O) maintenance treatment (mTx), which was approved by the FDA for the gBRCAm mPC patients who have not progressed on at least 16 weeks of a 1L plat regimen. Objective: To evaluate the health outcomes of gBRCA testing and treatment strategies among mPC patients using simulation model. **Methods:** A 3-state partitioned survival model was developed to assess the lifetime (20 year) health outcomes among treatment naïve mPC patients for the following strategies: 1. No gBRCA testing, no O mTx; 2. gBRCA testing before 1L, no O mTx; 3. gBRCA testing before 1L, O mTx; 4. gBRCA testing after 1L, O mTx. Without gBRCAm information before 1L (i.e., strategy 1&4) or if gBRCA negative, 45% mPC patients with good performance status (PS) and 27% with poor PS received 1L plat. We assumed that for gBRCAm patients, if known, 90% with good PS and 50% with poor PS received 1st line plat (i.e., strategy 2&3) in the base case. We assumed gBRCA testing had 100% of sensitivity and specificity. OS and PFS survival curves were extrapolated from pivotal trials. The additional health outcome benefit from O mTx after 16 weeks were modeled using efficacy from POLO trial. Health outcomes were measured by life years (LY) and, after applying health utilities by health state, quality adjusted life years (QALY). **Results:** The proportion of gBRCAm mPC patients receiving O mTx were 58.7% (4.4% of mPC patients) for strategy 3 vs 30.0% (2.2% of mPC patients) for strategy 4. For gBRCAm mPC patients, no testing generated the least LY and QALY, while testing before 1st line with O mTx resulted in the most. This trend was also observed in the overall cohort of mPC patients with the best outcomes from testing before 1st line with O mTx and worse outcomes from no testing or testing after 1st line with O Mtx. These survival gains are primarily derived by higher proportion of patients on platinum with better survival along with O Mtx gains. **Conclusions:** mPC patients achieve the highest health benefits by gBRCA testing before 1L treatment followed by O mTx, even with less than 5% mPC patients becoming eligible for O mTx (strategy 3). Research Sponsor: Merck and Astrazeneca.

Health outcomes of mPC patients from the strategies.

	Per Patient	Strategy 1	Strategy 2	Strategy 3	Strategy 4
mPC with gBRCAm Mean LY (95% CI for LYs)	LY	0.95 (0.84 – 1.10)	1.20 (1.01 – 1.44)	1.45 (1.11 – 1.78)	1.08 (0.90 – 1.26)
	QALY	0.73 (0.64 – 0.84)	0.92 (0.78 – 1.10)	1.15 (0.90 – 1.40)	0.85 (0.71 – 0.98)
Overall mPC (mix of gBRCAm and gBRCA neg) Mean LY (95% CI for LYs)	LY	0.96 (0.86 – 1.12)	0.98 (0.87 – 1.14)	1.00 (0.89 – 1.16)	0.97 (0.86 – 1.13)
	QALY	0.74 (0.66 – 0.86)	0.76 (0.68 – 0.88)	0.77 (0.69 – 0.89)	0.75 (0.67 – 0.87)

538 **Poster Session**

Pathogenic germline mutations prevalence in Saudi patients with pancreatic ductal adenocarcinoma.

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Background: While the majority of pancreatic ductal adenocarcinoma(PDAC) cases are sporadic, about 10% related to familial and hereditary component. Multiple studies have shown that germline genetic testing regardless of family history for patients with PDCA is feasible and more likely to identify the carrier of pathogenic mutations. There is no data about the prevalence of pathogenic germline mutations in Saudi population. We aimed to study the prevalence of these mutations in Saudi patient patients with PDAC regardless of the family history of cancer. **Methods:** By using our cancer genetics database, we analyzed all the confirmed cases of PDAC who were referred to the cancer genetic clinic at King Abdulaziz medical city in Riyadh, Kingdom of Saudi Arabia. Since November 2018, a comprehensive hereditary cancer gene panel (including 70 genes) is offered to all referred PDAC cases regardless of their family history of cancer after obtaining a genetic counselling assessment and an informed consent. **Results:** Between November 2018 and August 2021, a total of 88 patients with PDAC cases have been tested. The median age was 60 and the majority of patients were males (n=56, 64%). Most of the patients had stage IV disease (n=75, 85.23%). The genetic result was available for 86 patients. Pathogenic variant(PVs) was reported in 8.1% (n=7), variant of uncertain significance (VUSs) was reported in 15% (n=13) while no mutation reported in the rest of the patients. The PVs reported were BRCA2 (n=4), BRIP1 (n=1), PMS1(n=1) and MRE11 (n=1). All the carriers of the PVs had no documented family history of breast, ovarian or pancreatic cancers at the time of genetic counselling. **Conclusions:** This study confirms the importance of genetic testing in all patients with PDAC regardless of the family history. This is in line with previous studies from other populations. This is the first study from Saudi patients with PDAC and to the best of our knowledge, the first study in Arab population. Research Sponsor: None.

539 **Poster Session**

Pancreatic cancer detection using 5-hydroxymethylation signatures in plasma-derived cell free DNA in high-risk patients with new onset diabetes.

David Haan, Gulfem Guler, Anna Bergamaschi, Wayne Volkmuth, Samuel Levy; Bluestar Genomics, San Diego, CA; Bluestar Genomics, San Mateo, CA

Background: Pancreatic cancer (PaCa) is the third leading cause of cancer death in the United States despite a low incidence rate. It is often diagnosed when cancer has already metastasized to distant organs. Late diagnosis deprives patients of potentially curative treatments such as surgery and impacts survival rates. People with new onset diabetes (NOD) are at 6-8 fold increased risk for PaCa compared to the general population. Indeed, 0.85% of patients with NOD will be diagnosed with PaCa within 3 years. This population of PaCa patients with NOD constitute 25% of all new pancreatic cancer diagnoses. Surveillance of the NOD population for PaCa presents an opportunity to shift PaCa diagnosis to earlier stage. **Methods:** Whole blood was obtained from a cohort of 167 PaCa patients and 490 patients with cancers other than PaCa as well as 836 non-cancer controls with and without NOD. Plasma was processed to isolate cfDNA and 5hmC libraries were generated and sequenced. 5hmC data is used to generate models for PaCa detection using Bluestar Genomics's technology platform. **Results:** To investigate whether PaCa can be detected in plasma, we interrogated plasma-derived cfDNA hydroxymethylation in PaCa patients and non-cancer controls. Models trained using 5hmC-based biomarkers from cfDNA consistently performed with a mean test sensitivity of 61.1% [95% confidence interval (CI): 35.7% to 82.7%] and a test specificity of 97.6% (CI: 93% to 99.5%) measured across 50 cross validation iterations within the training data set, which was composed of 48.3% early stage (Stages I & II) disease. The final model was trained using all of the training data, yielding 58.4% (CI: 47.5% to 68.8%) sensitivity at 98% (CI: 96.5% to 99.0%) specificity. This model was then tested on an independent test set with 22 PaCa patients (51.7% early stage, 15 of which was NOD) and 123 non-cancer control patients (53 of which were NOD) and yielded a classification performance of 59.1% (CI: 36.4% to 79.3%) sensitivity at 95.9% (CI: 90.8% to 98.7%) specificity. The model performance in the subset of patient cohort with NOD was 53.3% (CI: 26.6% to 78.7%) sensitivity at 94.3% (CI: 84.3% to 98.8%) specificity. Lastly, sensitivity observed on an independent validation set, composed of 56 PaCa and 117 ITTP samples, was 46.4% (CI: 33.0% to 60.2%) with 100% (CI: 96.8 to 100%) specificity. **Conclusions:** Our results demonstrate PaCa detection in plasma-derived cfDNA using 5hmC profiles. Overall, the model performed consistently between the training and independent validation datasets. A larger clinical study is under development to clinically validate the model described in this study with the goal of identifying occult PaCa within the NOD population in order to enable earlier detection and thus improve patient outcomes. Research Sponsor: Bluestar Genomics.

540 Poster Session

Germline pathogenic variants among Mexican patients with adenocarcinoma of the pancreas.

Jose Luis Rodriguez Olivares, Yanin Chavarri Guerra, Jazmin Arteaga, Hector De la Mora Molina, Andrés Rodríguez-Faure, Ana María Hernández, Danielle Castillo, Jeffrey N. Weitzel; Olivares, Mexico City, Mexico; Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubirán, Mexico City, DF, Mexico; Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubiran, Ciudad De M Xico, Cdmx, Mexico; Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Delegacion Tlalpan, Mexico; Facultad de Medicina de la Universidad Autónoma de Coahuila, Torreón, Mexico; City of Hope Cancer Center, Duarte, CA; Oncogenetics for Precision Prevention, and Latin American School of Oncology, Sierra Madre, CA

Background: The reported frequency of germline pathogenic variants (PVs) in patients with pancreatic cancer is 8-10%. Depending on the setting, pancreatic cancer-associated germline PVs in the *BRCA* and *CDKN2A* genes are the most commonly detected. The mismatch repair genes (MMR; Lynch syndrome), *TP53, STK11, ATM* and *PALB2* are also associated with an increased risk of pancreatic cancer. The identification of PVs in patients with pancreatic cancer is important as there may be a benefit of targeted therapies, such as PARP inhibitors for cases with defective double strand break repair or response to immunotherapy with defective MMR and high tumor mutational burden. Additionally, identification of predisposing PVs can enable screening and prevention for other family members through cascade testing. According to international guidelines, all patients diagnosed with exocrine pancreatic cancer are candidates for genetic testing. However, there is an underrepresentation of ethnic/ racial minorities, including Hispanic patients, in genetic studies. **Methods:** Between April 2017 and May 2020, patients with diagnosis of pancreatic adenocarcinoma who were treated at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and enrolled in the international Clinical Cancer Genomics Community Research Network registry were included in this analysis. Genetic testing was performed by full sequencing of the following genes: *BRCA1, BRCA2, TP53, NF1, ATM, CHEK2, PALB2, CDKN2A, BRIP1, RAD50, RAD51C, RAD51D, MLH1, MSH2, MSH6, PMS2* and *EPCAM*, as well as multiplex ligation-dependent probe amplification for selected genes and *BRCA1* ex9-12del (Mexican founder mutation) screening with a three-primer polymerase chain reaction. Pedigrees, clinical and demographic data were obtained from the clinical records. **Results:** Forty-two patients with a diagnosis of pancreatic adenocarcinoma were included, with a median age at diagnosis of 57 years (range, 43-79), and 23/42 (55%) were women. The proportion of cases with operable, unresectable and metastatic disease at diagnosis was similar (33.3% for each group). The frequency of PVs was 11.9% (*ATM* n =2, *TP53* n =1, *PALB2* n =1 and *CHEK2* n =1). With a median follow-up 20 months 29/42 patients had died at the time of analysis (69%), the median overall survival was 16 months (range 3-84 months). No PVs were detected in the 4/42 patients who met the definition of familial pancreatic cancer (9.5%). **Conclusions:** Our results confirm the presence of PVs in cancer susceptibility genes in Mexican patients with pancreatic cancer, which is similar to that reported in other populations. However, it is notable that no *BRCA* PVs were identified in this small sample, as they are the most common PV found in other populations. Given to the heterogeneity of the PVs identified, our study supports the use of multi- gene panel testing in Hispanic patients with pancreatic cancer. Research Sponsor: None.

541 Poster Session

Initial observation of contrast profiles for 3D and 2D MRI sequences in MR-guided radiation therapy for locally advanced pancreatic cancer.

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Background: MR-guided stereotactic body radiation therapy (MR-SBRT) is a novel method of treating mobile tumors with soft-tissue gating and on-table adaptive planning. In our experience using the ViewRay MRIdian system (VR) for treating locally advanced pancreatic cancer (PA) with MR-SBRT, the true-fast imaging with steady-state free precession (TRUFI) sequences on the VR impart differing intensities for relevant structures seen on the pre-treatment high resolution 3D MRI (3D MRI) versus the real-time 2D cine MRI (2D cine) used for target tracking. Since these variations can confound target tracking selection, we propose that an understanding of the differing contrast profiles could improve selection of tracking structures and optimize treatment delivery. **Methods:** We retrospectively reviewed both 3D MRI and 2D cine images for patients (pts) with PA (n =20) treated on the VR. At simulation, an appropriate tracking target was identified and contoured on a single 3mm sagittal slice of the 3D MRI. This sagittal slice was directly compared to the registered 7mm 2D cine to identify structures with notable discrepancies in signal intensity. The 3D MRI was then explored in additional planes to confirm structure identities. For quantitative verification of the clinically observed differences, the pixel intensity distributions of 3D MRI and 2D cine DICOM image datasets were statistically compared. **Results:** In all pts reviewed, arteries (aorta, celiac, SMA) appeared with similar contrast profiles on both images. However, veins (portal vein, SMV) appeared hypointense on 3D MRI but hyperintense on 2D cine. Biliary structures appeared hyperintense on 3D MRI but only mildly hyperintense on 2D cine. The pixel intensity distributions extracted from 3D MRI and 2D cine images were confirmed to differ significantly (two sample Kolmogorov-Smirnov test; test statistic =0.40; p < 0.001). **Conclusions:** There are significant variations in image intensity between the initial treatment planning 3D MRI and the immediate pre-treatment 2D cine obtained with the VR. Understanding these discrepancies can guide radiation oncologists in choosing optimal tracking targets. Future work will focus on identifying the particular causes and frequencies of target tracking failures and exploring alternative tracking algorithms using artificial intelligence which could ultimately allow for VMAT on the ViewRay system. Research Sponsor: Department of Medicine Scholarship Enhancement in Academic Medicine (SEAM).

542   **Poster Session**

Differences in pretreatment frailty across gastrointestinal (GI) cancers in older adults: Results from the Cancer and Aging Resilience Evaluation (CARE) registry.

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Background: Frailty is an independent predictor of mortality in older adults and has been used to predict surgical complications and chemotherapy toxicities in GI cancers. How frailty differs between GI cancer types is unknown and could explain disparities in cancer outcomes. Our goal was to examine differences in pre-treatment frailty and geriatric assessment (GA) domain impairments between pancreatic, hepatobiliary, and colorectal cancers (CRC). We hypothesized that patients with more aggressive cancers (such as pancreatic cancer) would have increased frailty and more GA impairments, even prior to initiation of treatment. **Methods:** Our study included older adults age $\geq$60 years with cancer enrolled in the CARE Registry at the University of Alabama at Birmingham (UAB) who underwent a patient-reported GA during their initial visit with a GI medical oncologist. The GA was performed prior to any cancer-directed therapy. Frailty was defined using the 44-item CARE frailty index constructed based on principles of deficit accumulation described by Rockwood et al. We evaluated differences in frailty and GA domains between patients with CRC, pancreatic, and hepatobiliary cancers. Lastly, using a multivariable model we examined the adjusted odds ratio (aOR) of frailty by GI cancer type (reference CRC), adjusted for age, sex, race, cancer stage, and comorbidities. **Results:** Our study included 505 patients; 211 (41.8%) with CRC, 178 (35.2%) with pancreatic, and 116 (23.0%) with hepatobiliary cancers. Mean age of 70 years (standard deviation of 7) and 59% male. Cancer types did not differ by age, race, or sex. Patients with pancreatic and hepatobiliary cancers had more advanced cancer stage at time of assessment (stage IV 36.2% for CRC, 44.9% for pancreatic, and 45.2 for hepatobiliary; p=0.007). Older adults with pancreatic cancer had the highest prevalence of frailty (23.3% for CRC, 40.6% for pancreatic, and 34.3% for hepatobiliary; p=0.001), instrumental activities of daily living limitations (50.2% for CRC, 64.3% for pancreatic, and 52.7% for hepatobiliary; p=0.018), and malnutrition (40.8% for CRC, 70.3% for pancreatic, and 45.4% for hepatobiliary; $p<$ 0.001). In multivariable analyses, older patients with pancreatic cancer had a 2.0 times higher odds of frailty in comparison to patients with CRC (aOR 2.0 95% CI 1.2-3.3, p=0.007). **Conclusions:** Older adults with pancreatic cancer had a higher prevalence of pre-treatment frailty, malnutrition, and functional impairments compared to CRC and hepatobiliary cancers. A focus on early intervention in these patients with optimization of nutrition and targeted physical/occupational therapy prior to and during treatment may help mitigate these factors and potentially improve outcomes. Research Sponsor: U.S. National Institutes of Health.

543   **Poster Session**

Predictors of early mortality in early and late onset pancreatic cancer (PC).

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Background: The incidence of early-onset PC (EOPC) is rising and is associated with substantial mortality. We sought to identify independent predictors of early mortality in a cohort of EOPC and matched older patients (pts). **Methods:** Pts with EOPC (≤50 years) and matched cohorts of average (51-69, AOPC) and late (≥70, LOPC) onset PC by sex, race, year of diagnosis, and presence of metastatic disease were identified using the institutional tumor registry for years 2011-2018. Demographic and clinicopathologic characteristics were retrieved. Overall time of survival was assessed using Kaplan-Meier curves and the Cox Proportional Hazards modeling. Multivariable regression was conducted to evaluate for predictors of early mortality in non-metastatic and metastatic pts, defined as either death within six months of diagnosis compared to those surviving at least 12 months. **Results:** In total, 100 pts with EOPC (median age 47, range 29-50), 100 pts with AOPC (median age 60, range 51-69), and 100 pts with LOPC (median age 78, range 70-93) were analyzed. Of these, 46% were female, 28% were black, and 43% had metastatic disease at presentation. In non-metastatic pts, the 12-mo. survival rate by age group was: EOPC 74.4% (95% CI 59-85), AOPC 60% (95% CI 43-73), and LOPC 32.4% (95% CI 18-47). Variables associated with mortality within 6 months of diagnosis in non-metastatic pts on univariable analysis included age group, BMI ≤25, ECOG performance status (PS), neutrophil-to-lymphocyte ratio ≥5 (NLR5), CA 19-9 ≥130, no surgical resection, and no adjuvant chemotherapy. Multivariable regression confirmed no surgical resection (Odds Ratio [OR] 9.6, 95% CI 3-29), no receipt of chemotherapy (OR 6.9, 95% CI 2-21), and NLR5 (OR 5.4, 95% CI 1-22) as independent predictors for early mortality in non-metastatic pts. In metastatic pts, the 12-mo. survival rate by age group was: EOPC 32.6% (95% CI 19-47), AOPC 27% (95% CI 15-41), and LOPC 5.8% (95% CI 1-16). On univariable analysis, variables associated with mortality within 6 months of diagnosis included age group, ECOG PS, and NLR5. Multivariable regression confirmed LOPC (OR 11.6, 95% CI 2-61) and NLR5 (OR 11, 95% CI 2-54) as independent variables for early mortality. Race, sex, BMI, CA 19-9, smoking, alcohol use, primary tumor location, and site of metastases were not associated with early mortality in metastatic pts. No difference in independent predictors of early mortality between EOPC and older pts were identified. **Conclusions:** In this cohort of EOPC and matched older pts, LOPC (age ≥70) and NLR5 were independently associated with early mortality by 6 months in metastatic pts. In non-metastatic pts, lack of curative intent surgery, no receipt of chemotherapy, and NLR5 were independently associated with early mortality. There were no independent predictors for early mortality that distinguished EOPC and older pts. Further work is needed to identify prognostic factors unique to EOPC. Research Sponsor: None.

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544 **Poster Session**

Palliative care and end-of-life care in metastatic pancreatic cancer.

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Background: Patients with metastatic pancreatic cancer (mPC) have a 5-year survival of 2.7%. Studies have shown that patients with mPC receive aggressive end of life (EOL) care which has been associated with worse quality of life for patients and high use of resources when they are least likely to benefit patients. **Methods:** A retrospective database of patients with mPC treated at Fox Chase Cancer Center between 2010 and 2019 was analyzed for utilization of palliative care and EOL care. Statistical analysis was performed using one-sample Z tests calculated in Excel. **Results:** We identified 610 patients with mPC, of whom 39% received palliative care, 56% were referred to hospice, and 91.8% are deceased. The average time from mPC diagnosis to palliative care consult was 232 days, the average time from palliative care consult to death was 121 days. Patients who received palliative care were less likely to receive chemotherapy within 14 days of death (7.7% vs 13.3%, p =0.05), more likely to have a DNR code status (83.3% vs 44.5%, p < 0.0001), and more likely to be referred to hospice (83.9% vs 35.9%, p < 0.0001). The average length of time on hospice was 24 days with no difference between those who received palliative care and those who did not. Patients who were referred to hospice were also less likely to receive chemotherapy within 14 days of death (6.7% vs 19.8%, p < 0.0001). **Conclusions:** Patients with mPC who had a palliative care team involved in their care were significantly less likely to receive aggressive EOL care. Research Sponsor: Temple University Hospital Internal Medicine Resident Research Award.

545 Poster Session

Potential serum protein biomarkers of cancer cachexia, muscle atrophy, and survival in pancreatic ductal adenocarcinoma.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of death in the United States. Treatment is difficult and often complicated by the presence of cachexia, a systemic wasting condition affecting most PDAC patients at diagnosis. Skeletal muscle atrophy is a hallmark of cachexia and predicts outcomes after surgery and chemotherapy. In this study, we sought to identify possible serum biomarkers of cachexia, which correlates with changes to lean body mass and survival, using an aptamer-based platform in patients with PDAC. We hypothesize that unique proteins associate with cachexia and survival measures. **Methods:** Using SomaScan we measured the serum levels of 4,006 proteins in 21 patients with PDAC undergoing curative surgery. Clinical data and anthropometric measurements derived from pre-operative CT imaging were compared to protein levels with Spearman correlational analyses and logistic regression. We then queried DAVID Bioinformatics database to identify enriched functional protein categories. **Results:** Mean age was 66.9 ± 8.91 years, and mean bodyweight loss in the six months preceding diagnosis was $12.6 \pm 8.80\%$. Using consensus guidelines considering percent weight loss and skeletal muscle mass and radiation attenuation, 10 subjects (46.7%) were defined as "cachectic." We found 241 proteins significantly correlated to Cancer Weight Loss Grade (a composite measure of percent body weight loss and body mass index). High IDUA, CTLA4 and USE1, in particular, predicted the worst weight loss grade with 75% sensitivity and 92% specificity (AUC = 0.8894, odds ratio: 36, $p = 0.0068$). Four additional proteins significantly correlated with skeletal muscle index (CK-MM, CK-MB, PCOC2 and ADH4) while 13 proteins significantly correlated with muscle radiation attenuation. Lastly, we identified 18 proteins that significantly correlated with survival quartile. Of these, we found that elevated HS6ST2 and DEPP significantly predicted early recurrence and death compared to those with lower levels (medial survival: 177 days v. 850 days, $p = 0.0049$). Of the correlative proteins, enriched gene ontology terms included signal peptide (28.2), cytokine (6.86), negative regulation of endopeptidase activity (3.39), and immunoglobulin domain (3.24). **Conclusions:** Cancer cachexia in PDAC and various gastrointestinal malignancies remains a key clinical issue. While there are no definitive biomarkers currently in use to diagnose and manage cachexia preemptively, we present several potential candidates in a small cohort of patients. Ultimately, such assays may better elucidate common cachexia-inducing pathways, a shared spectrum of biomarkers and allow for the development of more specific therapies targeting cachexia. Research Sponsor: U.S. National Institutes of Health.

546 **Poster Session**

Clinical relevance of adjuvant chemotherapy in patients with pancreatic ductal adenocarcinoma who underwent surgery following neoadjuvant modified FOLFIRINOX.

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Background: The benefit of adjuvant chemotherapy (ACT) following curative-intent surgery in pancreatic ductal adenocarcinoma (PDAC) patients who had received neoadjuvant modified FOLFIRINOX (mFOLFIRINOX) remains unidentified. This retrospective analysis aimed to assess the clinical relevance of ACT in patients who underwent surgery following neoadjuvant mFOLFIRINOX. **Methods:** Between January 2017 and December 2020, 220 patients received neoadjuvant mFOLFIRINOX and underwent pancreatectomy for localized PDAC at the Asan Medical Center, Seoul, Korea. Patients unable to undergo curative-intent surgical resection (R0 or R1) and those with histological types other than ductal adenocarcinoma were excluded. Survival outcomes were compared according to ACT administration. Disease-free survival (DFS) was defined as the duration between surgery and recurrence or death of any etiology, whichever occurred first; and overall survival (OS) was that between surgery and death from any etiology. **Results:** ACT was administered to 150 (68.2%) patients. ACT recipients were significantly younger (median age, 61 vs. 64, $p = 0.035$) and they received significantly fewer cycles of neoadjuvant chemotherapy (median, 7 vs. 9, $p = 0.0001$) compared to non-recipients. As ACT, mFOLFIRINOX (n = 98, 65.3%), gemcitabine monotherapy (n = 39, 26.0%), and gemcitabine-capecitabine (n = 4, 2.7%) were administered. ACT recipients showed significantly better survival outcomes compared to non-recipients; median DFS 13.4 months (95% CI, 10.7–18.8) vs. 8.3 months (95% CI, 4.9–16.0), respectively ($p = 0.0042$); and median OS 33.4 months (95% CI, 29.9–NA) vs. 23.8 months (95% CI, 17.9–NA), respectively ($p = 0.0021$). DFS and OS were significantly better in ACT recipients regardless of the lymph node (LN) status during surgery ($p = 0.033$ for DFS and $p = 0.027$ for OS in negative LN; and $p = 0.032$ for DFS and $p = 0.012$ for OS in positive LN). There was no significant difference in DFS ($p = 0.79$) and OS ($p = 0.49$) between mFOLFIRINOX and gemcitabine-based regimens. In multivariate analysis, ACT remained significant as a favorable prognostic factor (DFS, hazard ratio [HR] 0.43 (95%CI, 0.26–0.71, $p = 0.001$); OS, HR 0.33 (95%CI, 0.17–0.64, $p = 0.001$). **Conclusions:** In PDAC patients who underwent surgery following neoadjuvant mFOLFIRINOX, ACT may be associated with improved survival outcomes. Its benefit was not affected by the LN status and ACT regimens. Research Sponsor: None.

547   **Poster Session**

Adjuvant gemcitabine (GEM) versus gemcitabine plus capecitabine (GEMCAP) in resected pancreatic adenocarcinoma: A retrospective analysis.

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Background: For patients who underwent curative-intent upfront surgery, adjuvant chemotherapy is the current standard of care. The previous, randomized phase 3 ESPAC-4 study showed significantly improved overall survival (OS) with GEMCAP compared to GEM. However, this study was conducted in European countries and its implication in Asian patients has not been explored yet. We conducted a retrospective analysis to evaluate the efficacy and safety of GEMCAP compared to GEM regimen. **Methods:** Between January 2017 and December 2020, a total of 292 patients who received adjuvant GEM or GEMCAP after curative-intent surgery in Asan Medical Center, Seoul, Korea, were included in this retrospective analysis. **Results:** Adjuvant GEM and GEMCAP were administered in 161 patients (55.1%) and 131 patients (44.8 %), respectively. Compared the GEMCAP group, age of patients were significantly older in the GEM group (median 66 vs 63 yo, p = 0.025); otherwise, there was no significant difference in baseline characteristics between two groups. With the median follow-up duration of 39.4 months (95% CI 36.9 - 45.0 months) in GEM group and 39.4 months (95% CI 34.7-41.6 months) in GEMCAP group, the median OS was 36.8 months (95% CI 29.7-43.5 months) and 46.1 months (95% CI 31.5 months – not reached) in the GEM group and GEMCAP group, respectively (unadjusted HR 0.72, 95% CI 0.51-1.02, p = 0.065). The median recurrence-free survival was 14.3 months (95% CI, 12.9-17.7 months) and 17.0 months (95% CI, 13.3-28.8 months) in the GEM group and GEMCAP group, respectively (p = 0.52). In the GEMCAP group, hand-foot skin reaction (any grade, 15.27 % vs 0.62 %, p < 0.001), neutropenia (78.6% vs 67.7%, p=0.037) and thrombocytopenia (30.53% vs 20.5%, p=0.035) were more common in the GEMCAP group compared to the GEM group. In multivariate analysis, adjuvant GEMCAP was significantly associated with better OS compared to adjuvant GEM (adjusted HR 0.64, 95% CI, 0.44-0.91, p = 0.014). Otherwise, moderate or poor histologic grade, lymph node positive, positive resection margin, and elevated CA 19-9 levels (> median) were significantly associated with poorer OS. **Conclusions:** In this retrospective analysis for Korean patients, adjuvant GEMCAP showed consistent clinical outcomes shown in the ESPAC-4 trial. As mFOLFIRINOX is the new standard of care for medically fit patients with resected pancreatic adenocarcinoma, further evaluation of optimal adjuvant chemotherapy in daily practice is warranted. Research Sponsor: None.

549   **Poster Session**

Nal-IRI+5-FU/LV vs 5-FU/LV in metastatic pancreatic cancer: Additional safety report of randomized Japanese phase 2 trial.

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Background: Based on a phase II study conducted in Japanese metastatic pancreatic cancer (NCT02697058) and a global phase III study, nal-IRI obtained market authorization in March 2020 in Japan for "Unresectable pancreatic cancer after disease progression following cancer chemotherapy". After one year of practice, physicians have a sense that some of the safety profile of nal-IRI to be slightly different from conventional irinotecan. The purpose of this report is to explore additional points of the nal-IRI safety in the Japanese study. **Methods:** This analysis with the safety population of nal-IRI+5-FU//-LV group was done for the incidence, time to first onset (TTO), and time to resolution (TTR) for the events associated with 12 identified risks in the Risk Management Plan (RMP)(Table) and other selected GI toxicities. Prophylaxis used were also analyzed. **Results:** Myelosuppression (82.6%), diarrhoea (58.7%) and hepatic dysfunction (41.3%) were commonly reported of the 12 identified risks. The median (m) TTO of these TEAEs was 16 days (range: 6, 73), 9 days (1, 61), and 22days (2,325) respectively. As for the mTTR, it was 8.0 days (95% CI: 8.00, 9.00), 4.0 days (4.00, 8.00), and 40.0 days (9.00, -) respectively. For the myelosuppression, there were 4 patients who received G-CSF for the treatment of ≥ grade 3 myelosuppression. The 8 patients who experienced diarrhoea leading to dose reduction had no recurrence of ≥grade3 diarrhoea after intervention. For other GI toxicities, anorexia occurred in 28/46 patients (60.9%) with mTTO 4.0 days (range: 2, 132) and mTTR 12.0 days (95% CI: 6.00, 26.00). Summary of TTO for the events associated with identified risks in the RMP. * Intestinal obstruction, enteritis, disseminated intravascular coagulation, interstitial lung disease, ventricular extrasystoles are also included in the RMP but not observed. Discussion: This is the first report of nal-IRI safety profile details such as timing in Japanese patients. It is interesting to note that some TEAEs appear different in practice regarding TTR in comparison with conventional irinotecan. This difference can be due to the unique PK profile of nal-IRI as a result of utilizing liposomal technology but needs to be further elucidated. **Conclusions:** Although the TEAEs occurred with nal-IRI+5-FU//-LV were controllable with proper management in Japanese patients, some with prolonged toxicities should be carefully managed. Clinical trial information: NCT02697058. Research Sponsor: Servier.

Grouped Term	Number of subjects with an event (%) (N=46)	Median onset of first event (min;max) (days)
Myelosuppression	**38 (82.6)**	**16.0 (6;73)**
Diarrhoea	**27 (58.7)**	**9.0 (1;61)**
Hepatic Dysfunction	**19 (41.3)**	**22.0 (2;325)**
Infection	11 (23.9)	50.0 (5;273)
Infusion Reaction	5 (10.9)	106 (38;154)
Thromboembolism	2 (4.3)	86.0 (43;129)
Gastrointestinal haemorrhage	1 (2.2)	37.0 (37;37)
Acute Kidney Injury	3 (6.5)	53.0 (8;252)
Myocardial Infarction and Angina Pectoris	1 (2.2)	8.0 (8;8)

550   Poster Session

A prospective phase II study of biweekly S-1, leucovorin and gemcitabine in elderly patients with locally advanced or metastatic pancreatic adenocarcinoma.

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Background: A chemotherapeutic regimen for elderly patients with advanced pancreatic cancer is necessary because of the considerable toxicities associated with current standard regimens. A modified combination of gemcitabine, S-1, and leucovorin (GSL) was used as a first-line treatment for elderly patients with newly diagnosed locally advanced or metastatic pancreatic adenocarcinoma in a prospective, phase II, multicenter clinical trial (NCT03559348). **Methods:** Patients more than 70 years of age with ECOG performance status score 0-2 were treated with GSL. GSL was administered every 2 weeks, intravenous gemcitabine 800 mg/m^2 at a fixed-dose rate of 10 mg/m^2/min on day 1 and oral S-1 (80-120 mg/day) plus leucovorin 30 mg twice daily on days 1-7, until disease progression, withdrawal, or intolerable toxicities. The primary endpoint was progression-free survival (PFS). **Results:** Overall, 49 patients were enrolled into the trial between 10 July, 2018 and 25 March, 2020, with a median follow-up of 12.5 months. The data cut-off point was on 15 June, 2021. The median patient age at diagnosis was 76 years (range, 70–87 years), and thirty-two (65.3%) patients had metastatic lesions before GSL treatment. Patient frailty was evidenced by the Vulnerable Elders Survey (VES)-13 score (median 5, range 0-13) and Geriatric 8 (G8) score (median 10.5, range 3-15) at baseline. Among the 44 evaluable patients, 13 demonstrated a partial response (29.5%) and 24 presented with stable disease (54.5%). The median PFS was 6.6, 6.6, and 6.3 months, and OS was 12.5, 12.7, and 11.6 months for total population, patients with locally advanced disease, and patients with metastatic lesions, respectively. Patients had improved emotional function and global health status score during GSL treatment. The most frequent grade 3 or higher treatment-related toxicities included anemia (20.4%), decreased neutrophils (18.4%), decreased white blood cells (16.3%), and oral mucositis (12.2%). **Conclusions:** The GSL regimen results in impressive efficacy with tolerable toxicity in this group of frail patients. In addition, quality of life can be maintained during the treatment. GSL could be a treatment of choice for elderly patients with locally advanced or metastatic pancreatic cancer. Clinical trial information: NCT03559348. Research Sponsor: National Health Research Institute, Taiwan.

552 Poster Session

Salvage ablative radiation therapy for loco-regionally recurrent pancreatic ductal adenocarcinoma following surgical resection.

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Background: Dose escalated radiation therapy for localized pancreatic ductal adenocarcinoma (PDAC) is associated with improved outcomes (Reyngold, JAMA Onc, 2021). Overall survival (OS) and loco-regional failure (LRF) rates with ablative radiation therapy (A-RT) in unresectable PDAC approach those of surgery. Herein, we report outcomes of A-RT as loco-regional salvage after resection. **Methods:** A prospective database (2016 onward) has been maintained of all patients receiving A-RT at for PDAC. A-RT is defined as a biologically effective dose (BED) ≥ 96 Gy ($\alpha/\beta = 10$). We analyzed consecutive patients from June 2016 through January 2021 who received A-RT for isolated loco-regional recurrences after resection. Survival was calculated using the Kaplan-Meier method. **Results:** Sixty-nine patients (40 men, 29 women) with median age of 67 received A-RT for loco-regionally recurrent PDAC. At diagnosis of recurrence, median disease-free interval from time of initial resection was 15.6 months (range 6.2–82.7) and median CA 19-9 was 65 U/mL (range < 1–1087). Twenty-one patients (30%) received neoadjuvant chemotherapy prior to surgery: pancreaticoduodenectomy (57 patients, 83%) or distal pancreatectomy (12 patients, 17%). There was a negative resection margin in 55 patients (80%). Most had T1/T2 (61 patients, 88%) and node-positive disease (44 patients, 64%). Radiation fractionation ranged from 5-25 fractions (median 25) to a total dose of 50-75 Gy (median 75). Median follow up was 16.2 months from RT. Median OS was 26.5 months from diagnosis of recurrence and 20.7 months from time of salvage A-RT. Twelve- and 24-month OS were 78.5% (95% CI 66.3–86.7) and 40.3% (25.8–54.3), respectively. In-field local failure was 8.5% (0.3–36.0) at 12 months and 27.5% (5.2–57.0) at 24 months. Respective disease-free survival at 12 and 24 months were 32.9% (21.7–44.1) and 12.3% (5.7–21.6). Grade 3 or greater gastrointestinal bleeding (GIB) occurred in 7 patients (10%), including one grade 4 event while on anticoagulation and one grade 5 event in a patient with portal hypertension. **Conclusions:** A-RT achieves favorable OS and LRF outcomes in patients with PDAC and an isolated loco-regional recurrence after surgical resection. Research Sponsor: None.

553   **Poster Session**

A phase II study of nivolumab in combination with modified FOLFIRINOX for metastatic pancreatic cancer.

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Background: Although FOLFIRINOX and nab-paclitaxel plus gemcitabine have improved the survival of unresectable pancreatic cancer patients, high unmet medical needs still exist for the treatment of this cancer. Nivolumab has shown efficacy for multiple cancer types in not only its monotherapy but also combinations with conventional chemotherapies. This study aimed to assess the efficacy and safety of nivolumab in combination with modified FOLFIRINOX, which is one of the first line chemotherapy for pancreatic cancer. **Methods:** Thirty-one treatment-naïve patients with metastatic, unresectable/recurrent pancreatic cancer patients received nivolumab (480 mg, every 4 weeks) plus modified FOLFIRINOX (oxaliplatin 85 mg/m^2, levofolinate 200 mg/m^2, irinotecan 150 mg/m^2 and fluorouracil 2400 mg/m^2, every 2 weeks). The primary endpoint was objective response rate (ORR) (central assessment). Secondary endpoints were overall survival (OS), progression-free survival (PFS) (central assessment), safety etc. **Results:** The median duration of follow-up was 13.40 months. ORR was 32.3% (CR: 0.0%, PR: 32.3%) and the median duration of response was 7.36 (range 3.5-20.1+) months. Median OS and PFS were 13.40 (90% CI 10.87-15.24) months and 7.39 (90% CI 3.88-7.59) months, respectively. The 1-year survival rate was 54.8 (90% CI 39.1-68.1) %. The most frequently reported grade 3-4 drug-related adverse events were neutrophil count decreased (38.7%), decreased appetite (16.1%), hypokalemia (12.9%), febrile neutropenia (9.7%), nausea (9.7%) and white blood cell count decreased (9.7%). Adrenal insufficiency (3.2%) was observed as immune mediated adverse event. **Conclusions:** Nivolumab in combination with modified FOLFIRINOX had a manageable safety profile in patients with metastatic pancreatic cancer. Additional work is needed to determine the population who can benefit from the combination. Clinical trial information: JapicCTI-184230. Research Sponsor: ONO Pharmceutical CO.,LTD., Bristol Myers Squibb.

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554   **Poster Session**

Randomized phase 2 study of nivolumab with or without ipilimumab in combination with stereotactic body radiotherapy in patients with refractory metastatic pancreatic cancer (CHECKPAC).

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Background: Pancreatic ductal adenocarcinoma remains one of the most lethal diseases. Investigating novel treatment strategies for patients with metastatic pancreatic cancer (mPC) is crucial. The purpose of this phase II trial study was to evaluate the clinical benefit of nivolumab with or without ipilimumab in combination with stereotactic body radiotherapy (SBRT) in patients with mPC. **Methods:** Between November 2016 and December 2019, patients with refractory mPC were randomly assigned 1:1 to SBRT of 15 Gy with nivolumab or nivolumab/ipilimumab stratified by performance status. Primary endpoint was clinical benefit rate (CBR) defined as proportion of patients with complete or partial response (PR) or stable disease, according to RECIST 1.1. Simon's 2-stage phase II optimal design was used independently for both arms with CBR determining expansion to second stage. Secondary endpoints included safety, overall response rate, duration of response (DOR), progression free survival and overall survival (OS). Exploratory analyses included biomarkers related to immune response. **Results:** Eighty-four patients (41 SBRT/nivolumab and 43 SBRT/nivolumab/ipilimumab) received at least one dose of study treatment. CBR was 17.1% (95% CI, 8.0 to 30.6) for SBRT/nivolumab and 37.2% (95% CI, 24.0 to 52.1) for SBRT/nivolumab/ipilimumab. PR was observed in one patient in SBRT/nivolumab and lasted for 4.6 months. Six patients in SBRT/nivolumab/ipilimumab obtained a PR with a median DOR of 5.4 months (95% CI, 4.2 - not reached). All responders had mismatch repair proficient tumors. Grade 3 or higher treatment-related adverse events occurred in 10 (24.4%) patients in SBRT/nivolumab and in 13 (30.2%) patients in SBRT/nivolumab/ipilimumab. PD-L1 expression by tumor proportion score or combined positivity score of ≥1% was not associated with clinical benefit. On-treatment decrease in serum interleukin (IL)-6, IL-8 and CRP levels was associated with better OS. **Conclusions:** Clinical meaningful antitumor activity and a manageable safety profile were demonstrated after SBRT/nivolumab/ipilimumab in patients with refractory mPC. Clinical trial information: NCT02866383. Research Sponsor: BMS, BMS hasDanish Comprehensive Cancer Center "National collaboration in immune-radiotherapy" Grant No. 4-1612-236/2".

555 **Poster Session**

Pathogenic variants of homologous recombination repair-related genes in advanced pancreatic cancer and oxaliplatin-based chemotherapy: Prospective multicenter observational study.

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Background: The latest National Comprehensive Cancer Network Guidelines for pancreatic adenocarcinoma recommended platinum-based chemotherapy for the patients with germline *BRCA1/2* or *PALB2* variants based on retrospective studies. However, the association between the efficacy of oxaliplatin-based chemotherapy and homologous recombination repair (HRR)-related gene variants has not yet been evaluated in a prospective study. **Methods:** This was a multicenter, prospective, observational study. Key inclusion criteria were: histologically confirmed pancreatic adenocarcinoma or adenosquamous carcinoma; candidates for systemic chemotherapy or currently under systemic chemotherapy for unresectable disease; age $\geq$ 20 years; Eastern Cooperative Oncology Group Performance Status 0–2; formalin-fixed paraffin-embedded cancer tissue available for genomic sequencing; and adequate hematological, liver, and renal function. Patients were assessed with the next generation sequencing (NGS)-based ACT-repair panel (ACT genomics; Taipei, Taiwan). ACT-repair panel is accredited by College of American Pathologists and is designed to detect short variants (SVs) including substitutions, insertions, deletions, and copy number variants of 35 genes including 8 HRR-related genes (*ATM, ATR, BRCA1, BRCA2, PALB2, RAD51B, RAD51C, RAD51D*). The primary endpoint was the one-year overall survival rate (1yr-OS%) after the initiation of oxaliplatin-based chemotherapy in patients who harbored pathogenic HRR gene variants. On the basis of published retrospective data, expected 1yr-OS% was set at $\geq$ 60% in this study. **Results:** Forty patients were enrolled from August 2018 to March 2020. Median age was 67 years (range, 49–81 years). Sequencing data were obtained from 39 patients (NGS success rate = 97.5%). Nine patients (22.5%) harboring HRR gene; *ATM* SVs (n = 4), *BRCA2* loss of heterozygosity (LOH) (n = 3), *BRCA2* SVs (n = 1), and *PALB2* LOH (n = 1). Three patients received oxaliplatin-based chemotherapy as first-line chemotherapy, while the remaining six patients received it as second- or later-line oxaliplatin-based chemotherapy. The 1yr-OS% was 44.4%, and the median overall survival was 221 days (95% confidence interval, 79–NA days) after the initiation of oxaliplatin-based chemotherapy. In three patients who received oxaliplatin-based chemotherapy as first-line treatment, overall survivals were 703 (alive), 694 (alive), and 405 (dead) days, respectively. **Conclusions:** Efficacy of oxaliplatin-based chemotherapy on advanced pancreatic cancer harboring HRR-related gene variants did not meet the primary endpoint of 1yr-OS% ($\geq$ 60%). Clinical trial information: UMIN000033655. Research Sponsor: JSPS KAKENHI Grant Number 17K08413.

Outcomes of anlotinib plus nab-paclitaxel/gemcitabine as first-line treatment for patients with advanced pancreatic adenocarcinoma: A retrospective analysis in China.

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Background: Anlotinib, a novel small molecule multi-target tyrosine kinase inhibitor that can effectively inhibit VEGFR, PDGFR, FGFR, C-KIT et al, is proved to have anti-tumor angiogenesis and tumor growth inhibition effects. However, Anlotinib exploration on advanced pancreatic adenocarcinoma (PDAC) is still limited. The motivation of this work is to evaluate the efficacy and safety of anlotinib combined with nab-paclitaxel/gemcitabine in the first-line treatment of patients with advanced PDAC, and provide some evidence for the treatment regimens of advanced PDAC. **Methods:** This was a retrospective study in patients with advanced PDAC performed from Aug 17, 2019 to Apr 3, 2021. Patients who received anlotinib plus nab-paclitaxel/gemcitabine treatment were defined as Group 1, and patients who received nab-paclitaxel/gemcitabine as Group 2. The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (P2021-13-21). The response to treatment was evaluated according to RECIST version 1.1. In addition, adverse events were evaluated by CTCAE v5.0. **Results:** In this work, 33 patients were included, with 17 cases in Group 1 and 16 cases in Group 2. The median PFS (mPFS) of Group 1 and Group 2 were 5.0 (95% CI, 4.97-5.94) months and 2.7 (95% CI, 2.4-3.3) months, respectively ($P = 0.0220$). The median OS (mOS) of Group 1 and Group 2 were 9.0 (95% CI, 6.55-11.45) months and 6.0 (95% CI, 1.08-10.92) months, respectively ($P=0.006$). The PFS rate in 3 and 6 months and the OS rate in 6 and 12 months of Group 1 were significantly higher than that of Group 2. The most common grade 3 treatment related AEs (trAEs) were hematological toxicity, with 35.29% in Group1 and 31.25% in Group 2. Non-hematological toxicity were hypertension, hand-foot syndrome and diarrhea. No grade 3 or higher non-hematologic toxicity was observed in all patients. **Conclusions:** Anlotinib plus nab-paclitaxel/gemcitabine as first-line treatment demonstrates encouraging efficacy and manageable AE in patients with advanced PDAC. Clinical outcomes are improved with longer PFS and OS in anlotinib plus chemotherapy group. More data are needed to confirm the long-term efficacy and safety of anlotinib plus nab-paclitaxel/gemcitabine in advanced PDAC patients. Research Sponsor: None.

A phase 1b study evaluating IL-1β and PD-1 targeting with chemotherapy in metastatic pancreatic cancer (PanCAN-SR1).

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Background: Pancreatic ductal adenocarcinoma (PDA) is a highly lethal malignancy that is refractory to therapeutic targeting of the immune microenvironment. In preclinical work, IL-1β was shown to be upregulated in pancreatic cancer tumors, and in mouse models, IL-1β expression led to activation of pancreatic stellate cells and immunosuppression (Das et al 2020). We hypothesize that blockade of IL-1β and PD-1 will result in alterations in myeloid, lymphoid, and fibroblast subsets within the pancreatic cancer microenvironment and add therapeutic benefit in combination with chemotherapy in PDA. **Methods:** We are conducting an open-label multicenter Phase Ib study evaluating a 4 drug regimen including gemcitabine and nab-paclitaxel with the addition of canakinumab (ACZ885), a high-affinity human anti-interleukin-1β (IL-1β) monoclonal antibody (mAb), and spartalizumab (PDR001), a mAb directed against human Programmed Death-1 (PD-1). Eligible subjects have metastatic PDA without prior anti-cancer therapy for metastatic disease and RECIST measurable disease. The primary objective was to identify a recommended phase II/III dose of combination therapy by evaluating the incidence of dose limiting toxicities in the first 56 days (8 weeks) of dosing in at least 6 evaluable subjects utilizing a Bayesian logistic regression model. All subjects underwent baseline and on-study tissue and blood collection for extensive exploratory correlative studies. Secondary objectives including safety and tolerability of quadruple therapy and preliminary assessment of clinical activity. **Results:** 10 subjects were enrolled between November 2020 and March 2021, and the first 6 subjects to complete 8 weeks of therapy were included in the dose confirmation analysis. There were no dose limiting toxicities and the recommended Phase II/III dose was established as; gemcitabine (1000 mg/m2 IV) on day 1,8,15; nab-paclitaxel (125 mg/m2 IV) on day 1,8,15, canakinumab (250 mg via subcutaneous injection) on day 1, spartalizumab (400 mg IV) on day 1; of each 28 day cycle. Adverse events were consistent with those seen with chemotherapy and were predominately hematologic. The majority of subjects completed the on-treatment blood and tissue collection for correlative analysis. The study is ongoing with subjects remaining on therapy and all subjects will be evaluated for efficacy. **Conclusions:** In this Phase Ib study, we demonstrated the feasibility and safety of adding canakinumab and spartalizumab to standard of care chemotherapy in first line metastatic PDA and established the recommended Phase II/III dose. This novel 4 drug combination will be tested in a randomized Phase II/III study through the Precision Promise clinical trial network. Preliminary correlative and efficacy data will be reported. Clinical trial information: NCT04581343. Research Sponsor: Pancreatic Cancer Action Network., Pharmaceutical/Biotech Company.

Neoadjuvant and adjuvant antitumor vaccination alone or combination with PD1 blockade and CD137 agonism in patients with resectable pancreatic adenocarcinoma.

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Background: Utilizing a vaccine that induces and activates host effector T cells and co-administering it with immune modulating agents that enhance anti-tumor T cell activity is a potential strategy for overcoming pancreatic adenocarcinoma's (PDA) resistance to immunotherapy. Our prior clinical trial demonstrated a GM-CSF-secreting, allogeneic tumor cell vaccine (GVAX) increases infiltrating CD8+ T cells in PDA. Follow up preclinical work demonstrated therapeutic synergy between GVAX and PD-1 inhibition (PD1) with efficacy further enhanced by CD137 agonism (CD137). **Methods:** This was a 3-arm trial of neoadjuvant & adjuvant GVAX-based therapy in resectable (r) PDA patients (pts). Adults with clinically resectable, untreated PDA were enrolled in 1 of 3 study treatments: Arm A (GVAX alone), Arm B (GVAX + PD1 [Nivolumab]), or arm C (GVAX + PD1 + CD137 [Urelumab]). Treatment was given as follows: Day 1 - Cyclophosphamide 200mg/m2 IV (All Arms), Nivolumab 480mg IV (Arms B, C), Urelumab 8mg IV (Arm C); Day 2 – GVAX ID (All Arms). Pts were treated at 3 timepoints: 1) once 2 weeks prior to surgery; 2) once post-surgical recovery prior to standard of care adjuvant chemotherapy (SOC); 3) every month (up to 4 mo) following completion of SOC (if disease-free). SOC regimes included (m)FOLFIRINOX, Gem +/- Cap/NAB-Paclitaxel. The study was powered for a primary biologic endpoint: treatment-related change in intratumoral CD8+CD137+ T cells. Clinical endpoints included disease-free survival (DFS: time from surgery to recurrence), overall survival (OS: time from surgery to death), and safety. **Results:** 38 pts (N = 15 [Arm A], N = 13 [Arm B], N = 10 [Arm C]) were eligible for efficacy analysis (had R0/R1 resection) and 45 pts (N = 17 [A], N = 17 [B], N = 11 [C]) were eligible for safety analysis (had ≥1 dose of study treatment). Demographics, surgical pathology features, and SOC durations were similar in all Arms. At median follow up of 23 mo [A], 26 mo [B], and 22 mo [C], median DFS (95% CI) was 14.82 mo (6.0, NA), 16.23 mo (7.49, NA) and not reached (16.33, NA) for Arms A, B, C, respectively. There was no DFS benefit to adding PD1 compared to GVAX alone (HR 0.98 [95% CI 0.42, 2.27], p = 0.96). Combination CD137 + PD1 + GVAX was associated with marginally significant improved DFS compared to GVAX alone (HR 0.38 [95%CI 0.12, 1.19], p = 0.097) and GVAX + PD1 (HR 0.38 [95%CI 0.12, 1.21], p = 0.103). Median OS (95% CI) was 25.0 mo (18.8, NA), 26.4 mo (20.3, NA), and not yet reached for Arms A, B, C, respectively. There were no serious adverse events. In Arm C, 1 pt had grade 3 rash that delayed treatment and there was 1 instance of grade 2 AST/ALT elevation. The biologic endpoint will be reported at the meeting. **Conclusions:** Despite a small sample size, combining GVAX with dual immune-targeting of PD-1 blockade and CD137 agonism was safe and may enhance DFS in rPDA pts treated in the perioperative and post-adjuvant settings. Clinical trial information: NCT02451982. Research Sponsor: Bristol-Myers Squibb (Rare Disease Program Grant)., U.S. National Institutes of Health.

Preliminary results of a phase 1 study of sea-CD40, gemcitabine, nab-paclitaxel, and pembrolizumab in patients with metastatic pancreatic ductal adenocarcinoma (PDAC).

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Background: SEA-CD40 is an investigational nonfucosylated IgG1 monoclonal agonistic antibody targeted to CD40, expressed on antigen-presenting cells. SEA-CD40 binds with increased affinity to $Fc\gamma RIIIa$ resulting in enhanced effector function and CD40 agonism, allowing amplification of immune stimulation and antitumor activity. PDAC can be treated with gemcitabine + nab-paclitaxel (GnP), often with poor survival. Combining chemotherapeutic agents with SEA-CD40 could facilitate robust antigen release and amplified presentation to CD8+ T cells. In preclinical models, the combination of SEA-CD40 and chemotherapy resulted in significant antitumor activity which is further enhanced with anti-PD1 treatment. We present data from an ongoing Phase 1 study (SGNS40-001) in a PDAC cohort evaluating the combination of SEA-CD40, GnP, and pembrolizumab (pembro). **Methods:** Patients (pts) ≥18 years old with untreated metastatic PDAC and Eastern Cooperative Oncology Group performance scores of 0 or 1 were enrolled. GnP were administered on Days 1, 8, and 15 of each 28-day cycle with 10 or 30 μg/kg SEA-CD40 IV on Day 3. Pembro was administered every 42 days starting on Day 8. **Results:** As of July 9, 2021, 61 pts were treated: 40 and 21 pts at 10 and 30 μg/kg SEA-CD40, respectively. Minimum follow-up was 5 months. The most frequent treatment-emergent adverse events (TEAEs) are shown in Table. 5 (8%) pts experienced an AE leading to treatment (tx) discontinuation (3 and 2 in 10 and 30 μg/kg SEA-CD40 dose, respectively), 35 (57%) pts experienced a serious TEAE (22 and 13 pts in 10 and 30 μg/kg, respectively). Two tx-related deaths occurred: colitis attributed to pembro, and septic shock attributed to GnP. Pts had transient increases in circulating cytokines and chemokines associated with immune activation and trafficking as well as increases in markers of activation on peripheral NK cells and T cells. **Conclusions:** The combination of SEA-CD40 + GnP + pembro demonstrated a tolerable safety profile. Evidence of immune activation was observed, consistent with the proposed mechanism of action. Follow-up for response and survival are ongoing. Clinical trial information: NCT02376699. Research Sponsor: Seagen Inc.

Summary of most frequent TEAEs (≥50% of pts) (SEA-CD40 + GnP + pembro).

Preferred Term	10 μg/kg (n=40)		30 μg/kg (n=21)		Overall (n=61)	
	Any grade	Grade≥3	Any grade	Grade≥3	Any grade	Grade≥3
Fatigue	31 (78%)	7 (18%)	17 (81%)	4 (19%)	48 (79%)	11 (18%)
Nausea	26 (65%)	1 (3%)	18 (86%)	1 (5%)	44 (72%)	2 (3%)
Neutropenia	26 (65%)	23 (58%)	15 (71%)	14 (67%)	41 (67%)	37 (61%)
Infusion related reaction	23 (58%)	4 (10%)	16 (76%)	1 (5%)	39 (64%)	5 (8%)
Chills	24 (60%)	0	14 (67%)	0	38 (62%)	0
Diarrhoea	23 (58%)	5 (13%)	13 (62%)	4 (19%)	36 (59%)	9 (15%)
Pyrexia	22 (55%)	1 (3%)	13 (62%)	1 (5%)	35 (57%)	2 (3%)

560   **Rapid Abstract Session and Poster Session**

Randomized phase III study of sintilimab in combination with modified folfrinox versus folfrinox alone in patients with metastatic and recurrent pancreatic cancer in China: The CISPD3 trial.

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Background: FOLFIRINOX or modified FOLFIRINOX (mFFX) is the standard of care for the first line treatment of metastatic pancreatic adenocarcinoma (PDAC). However, the prognosis still remains poor, novel treatment options are urgently need. Sintilimab, a human IgG4 monoclonal antibody that binds to programmed cell death receptor-1(PD-1), has shown remarkable efficacy in various cancers. We designed the CISPD3-trial in China, aimed to determine the efficacy and safety of the combination of Sintilimab and mFFX for metastatic or recurrent PDAC. **Methods:** In this single center, randomized, open-label, phase 3 trial, we enrolled patients with metastatic or recurrent PDAC to compare the efficacy and safety of Sintilimab combined with mFFX versus mFFX alone as first-line or second-line therapy. Patients eligible were randomly assigned (1:1) to Sintilimab (200 mg every 3 weeks) plus mFFX (irinotecan 85 mg/m^2, oxaliplatin 68 mg/m^2 followed by 5-FU 2400 mg/m^2, every 2 weeks) or mFFX. The primary endpoint was overall survival (OS), secondary endpoints included progression free survival (PFS), objective response rate (ORR), disease control rate (DCR) and safety. This study is registered with ClinicalTrials.gov, NCT03977272. **Results:** From March 2019, to Dec 2020, 110 patients were enrolled and randomized to Sintilimab plus mFFX (n = 55) or mFFX (n = 55). 85.5% Patients had metastatic disease and 14.5% had recurrent disease, 7.3% Patients had previous first-line chemotherapy. The baseline characteristics of the subjects in these two arms were comparable. The median follow-up time for OS was 21.3 months (IQR 15.9-25.0) in Sintilimab plus mFFX group and 19.6 months (15.5-25.1) in mFFX group. The median OS was similar between Sintilimab plus mFFX (10.9 months) and mFFX arm (10.8 months) with HR = 1.083 (95% CI 0.6843 to 1.690). Median PFS was 5.9 months in Sintilimab plus mFFX arm and 5.73 months in mFFX arm (HR 0.9324, 95% CI, 0.6158 to 1.412). The ORR was 50% in the Sintilimab plus mFFX arm versus 23.9% in the mFFX arm (P = 0.010). The most common AE of Grade $\geq$ 3 are neutropenia (58.5% in the Sintilimab plus mFFX group vs. 44.4% in mFFX group), thrombocytopenia (17.0% vs. 11.1%), anemia (13.2% vs. 13.0%), vomiting (13.2% vs. 11.1%), increased aminotransferase (11.3% vs. 5.6%). 22.6% immune-related adverse events (irAEs) and 5.7% irAEs of grade $\geq$ 3 were observed in Sintilimab plus mFFX arm. The most common irAEs were pulmonary adverse event (13.2%) with 3 (5.7%) patients grade $\geq$ 3, among which 1 (1.8%) death was considered to be treatment-related. No new safety signals were identified. **Conclusions:** The addition of Sintilimab to mFFX improved ORR in advanced PDAC patients significantly, however no superior OS and PFS were observed. Toxicity was manageable. These data suggest that combined PD-1 blockade may expand the benefit of chemotherapy in PDAC. Clinical trial information: NCT03977272. Research Sponsor: None.

561   **Poster Session**

Machine learning for tracking planned versus delivered dose in pancreas SBRT.

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Background: Cone-beam CT (CBCT) used for daily image guidance in pancreatic stereotactic body radiotherapy (SBRT) is fraught with imaging artifacts leading to poor visualization of target and avoidance structures. Machine learning methods can be used to generate synthetic CT (sCT) images from CBCT to eliminate imaging artifacts. We sought to compare planned versus delivered radiation dose to luminal GI organs at risk (OARs) during pancreas SBRT using sCT. **Methods:** Previously treated patients from a single institution were eligible if treated with 5 fractions of pancreas SBRT using daily CBCT and inspiration breath hold. CBCT-based sCT was generated for each treatment fraction using our previously reported cycleGAN technique. Physicians manually contoured GI OARs (stomach, duodenum, and bowel [remaining small bowel and large bowel]) on sCTs. Rigid online registration from treatment was used to re-calculate the delivered dose on each sCT. Fractional delivered dose to OARs was compared to planned dose and dose constraints with descriptive statistics. Max dose to 1cc or 20cc of an OAR was defined as D1cc and D20cc respectively. **Results:** 7 patients and 35 cumulative SBRT CBCT datasets were included. The median SBRT cumulative dose was 8 Gy x 5 fractions (40 Gy total). Each GI OAR was constrained per fraction to D1cc < 7 Gy (cumulative D1cc < 35 Gy) and D20cc < 4 Gy (cumulative D20cc < 20 Gy) during SBRT planning. Table shows the estimated OAR delivered doses on each sCT compared to planned doses and dose constraints. Each patient had at least 1 fraction that exceeded a planned GI OAR dose; 2 patients had delivered dose to 1cc of duodenum exceeding constraint for all 5 fractions. After a median follow-up of 9 months (range 5-34), there were 2 CTCAE Grade 1 and no Grade 2+ GI toxicity events possibly or likely related to SBRT. **Conclusions:** Physician contouring and dose calculation using CBCT-based sCT was feasible. Estimated delivered doses of pancreas SBRT generally exceed planned doses. Further study of sCT in pancreas SBRT is warranted for improved localization, dose calculation, and adaptive radiotherapy. Research Sponsor: None.

Structure		Mean Planned Single Fraction Dose (Gy)	Median % Difference Delivered vs Planned	Fractions Exceeding Planned Dose	Fractions Exceeding Constraint
Duodenum	D1cc	4.2	+19%	28/35	16/35
	D20cc	2.2	+7%	21/35	0/35
Stomach	D1cc	2.8	-3%	17/35	8/35
	D20cc	1.2	+25%	22/35	0/35
Bowel	D1cc	3.5	+15%	26/35	9/35
	D20cc	2.1	+21%	28/35	2/35

562   **Poster Session**

Randomized phase II trial of neoadjuvant chemotherapy with modified FOLFIRINOX versus modified FOLFIRINOX and PD-1 antibody for borderline resectable and locally advanced pancreatic cancer (the CISPD-4 study).

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Background: Neoadjuvant chemotherapy is recommended for BRPC and LAPC planned resection. PD-1 antibody alone was failed in advanced pancreatic cancer, but chemotherapy combined with PD-1 antibody are promising. **Methods:** This is a randomized, controlled, open-label phase II study including patients with BRPC or LAPC. Modified FOLFIRINOX (mFFX) is used as neoadjuvant chemotherapy. Patients will be randomly allocated into two groups: mFFX group and mFFX plus PD-1 antibody group (PD-1 group). Imaging evaluation will be discussed by the MDT. Surgical resection will be performed if the MDT confirms the resectability. (NCT03983057). **Results:** From March 4, 2019 to August 1, 2021, 146 patients (62 BRPCs and 84 LAPCs) were enrolled. 115 patients received at least four cycles of therapy. In PD-1 group, irAEs happened in seven patients (9.7%), including rash (3 patients, Grade 1), hepatic AE (2 patients Grade 3, 1 patient Grade 2), renal AE (2 patients, Grade 2), and hyperglycemia (2 patients). Radiological PR were noted in 13.3% patients in mFFX group, and 26.9% in PD-1 group. For BRPC patients, the radiological PR was 13.0% and 36.3%, respectively. The resection rate was similar in two groups (47.4% and 51.7%). R0 resections were performed in 70.3% and 86.6% patients, respectively. For LAPC patients, PD-1 group has a higher resection rate (37.1% vs. 48.0%). The survival data are not mature at present. **Conclusions:** Modified FOLFIRINOX plus PD-1 antibody is feasible and well-tolerated for BRPC and LAPC patients. The study will be continued and the detailed data will be reported. Clinical trial information: NCT03983057. Research Sponsor: key clinical study foundation of the First Affiliated Hospital, Zhejiang University School of Medicine.

563 Poster Session

A phase I study of pharmacokinetic (PK)-driven sequential dosing of rucaparib (RUB) with irinotecan liposome (nal-IRI) and fluorouracil (5FU) in metastatic gastrointestinal (mGI) and pancreas (PANC) cancers.

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Background: RUB is an oral PARP1,2,3 inhibitor that demonstrated efficacy in patients (pts) with ovarian and prostate cancers harboring deleterious BRCA mutations. RUB exerts synergistic anti-tumor effect with IRI preclinically though the combination has overlapping toxicities. We previously published on the population PK of nal-IRI (Adiwijaya, Ma et al, Clin Pharm Ther 2017). We conducted a phase I study to evaluate a novel sequential dosing of RUB with nal-IRI/5FU in mGI cancer pts. **Methods:** Eligible pts had incurable mGI cancer previously received > 1 line of therapy (rx), ECOG PS 0-1, had RECIST measurable disease, adequate organ reserves and not received IRI for metastatic disease. Previous PARPi rx was excluded. The endpoints included dose limiting toxicity (DLT), maximum tolerated dose (MTD) and toxicity profile. The dose escalation utilized the 3+3 design. RUB was given oral bid on Day 4 to 13 and 18 to 27 with nal-IRI i.v. and 5FU i.v. 2400 mg/m2 over 46 hr on Day 1 and 15, every 28 day. Planned dose levels were RUB 400 mg/nal-IRI 50 mg/m2 (DL1), 400 mg/70 mg/m2 (DL2) and 600 mg/70 mg/m2 (DL3). Adverse events (AEs) were scored per CTCAE v4.03. Molecular profile was evaluated by CLIA-certified NGS testing. **Results:** Eighteen pts including 11 colorectal (CRC), 6 PANC, 1 gastroesophageal (GE) were enrolled and 12 were evaluable for DLTs. DL2 was not tolerable (DLT: G3 diarrhea, nausea and vomiting) and DL2A was added (RUB 600 mg/nal-IRI 50 mg/m2). DL2A enrolled 6 pts with no DLT and was determined as the MTD. Of DLT-evaluable pts, G3 and worse treatment-related AEs from all cycles were diarrhea (33%), fatigue (25%), leukopenia (25%), neutropenia (25%), anemia (8%) and nausea (8%). Four of 12 response evaluable pts had partial response: 2 CRC (1 had *ATM* mut), 1 PANC (*ATM* mut), 1 GE (*BRCA2* mut) whilst 3 responders previously had platinum (PLA). Five pts had stable disease beyond 16 weeks (range 18.9 to 100.7 weeks), and all had prior PLA. **Conclusions:** The study successfully determined the MTD of RUB in combination with nal-IRI and 5FU. Encouraging efficacy was observed in PLA-treated mGI cancers including responses in those harboring *ATM* and *BRCA* alterations. The study is proceeding to evaluate the efficacy of the combination in metastatic pancreas cancer pts with and without BRCA1/2 or PALB2 alterations. Clinical trial information: NCT03337087. Research Sponsor: Ipsen, Clovis Oncology.

A phase II study of niraparib and dostarlimab with radiation in patients with metastatic pancreatic cancer.

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Background: PARP inhibitors have activity as monotherapy in BRCA1/2 mutated metastatic pancreatic cancer; however, several other genes and associated proteins exist in the homologous recombination repair (HRR) pathway promoting resistance to chemotherapy and radiation-induced damage. Tumors with HRR deficiency have an impaired ability to repair themselves and are susceptible to PARP inhibition, but ionizing radiation can also induce DNA breaks. Ongoing research suggests that PARP inhibitors may cause radio-sensitization and may also enhance sensitivity to immunotherapy. We conducted a phase 2 study of niraparib and dostarlimab with radiation in a biomarker unselected PDAC population given PARP inhibitors' immunomodulatory and radiosensitizing effects. **Methods:** In this open-label, single-arm, phase-2 study, eligible patients had histologically confirmed MSS PDAC, ECOG PS 0-1, and progressed on at least one line of jm. Treatment consisted of niraparib 200 mg daily on a 21-day cycle, dostarlimab 500 mg every 3 weeks every 4 weeks for the first four doses, then 1000 mg every 6 weeks, and 3 fractions of 8 Gy at Cycle 2. Treatment continued until progressive disease, discontinuation, or withdrawal. The primary endpoint was DCR by RECIST 1.1 with radiological evaluations every 3 months. Secondary endpoints included DCR by irRECIST, PFS, OS, and safety. Responses were defined as disease control outside the radiation field. We obtained serial tumor biopsies, including pre-treatment. A two-stage design was used, requiring disease control in at least one of the first 15 patients before proceeding to the full accrual of 25 patients. Intention to treat analysis included all patients receiving at least one dose of any study agent. **Results:** We enrolled and treated 15 pts (median age 60 years [range 37-77], 53% male) from 08/2020 to 05/2021. Overall, DCR was 0/15 (95% CI: 0-22%), median PFS was 1.6 months (95% CI: 1.1-2.7), and median OS 3.1 months (95% CI: 1.5-7.7). Among 27 treatment-related serious adverse events, 15 (56%) were grade 3, including decreased CD4 lymphocytes, thrombocytopenia, anemia, and fatigue being the most common. **Conclusions:** The combination of niraparib and dostarlimab with radiation did not meet the pre-specified criteria for expansion to full accrual. Further analyses of dose intensity in this heavily pretreated and evaluation of in-field responses are underway. Further investigation of the combination with biomarker selection is warranted. Clinical trial information: NCT04409002. Research Sponsor: GSK.

565   **Poster Session**

Neoadjuvant gemcitabine, docetaxel, and capecitabine results in comparable surgical outcomes to modified FOLFIRINOX in patients with pancreatic ductal adenocarcinoma who also receive radiation: A single institution experience.

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Background: Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis with a minority of patients (pts) eligible for curative resection. Currently, systemic treatment options for down-staging pts with borderline resectable or locally advanced PDAC is extrapolated from the metastatic setting and modified FOLFIRINOX (FFX) +/- radiation (RT) is the most widely used regimen. Herein, we report the outcomes of combination gemcitabine, docetaxel, and capecitabine (GTX) +RT as compared to FFX +RT in the neoadjuvant (NA) setting via a single institution retrospective cohort review. **Methods:** We retrospectively reviewed the outcomes of pts with PDAC who underwent surgical resection at Columbia University Irving Medical Center (CUIMC) between 2011-2020. We evaluated demographics, treatment, clinical, surgical, and pathological outcomes. Statistical analysis includes Kaplan-Meier analysis and paired t-tests. **Results:** We reviewed 717 pts who underwent surgical resection at CUIMC of which 227 pts were confirmed to have received NA chemotherapy. Of those 227 patients, 133 pts also received RT. In total, 39 pts received GTX+RT and 42 pts received FFX+RT. Median age at diagnosis of pts who received NA GTX+RT or FFX+RT was 65 and 63 years, respectively. All pts were AJCC stage III at diagnosis and ECOG 0 or 1. There was a significantly greater percentage of pts who achieved R0 resection after GTX+RT as compared to FFX+RT, 35 (89.7%) vs 29 (69.0%), respectively (p=0.022). Significantly more pts achieved N0 lymph node status after GTX+RT as compared to FFX+RT, 29 (74.4%) vs 22 (52.4%), respectively (p=0.041). No statistically significant difference was detected in recurrence-free survival (RFS) or median overall survival (mOS) in pts who received GTX+RT and achieved R0 resection as compared to FFX+RT. See Table for summary. **Conclusions:** GTX appears to be a viable and active NA regimen in Stage III PDAC. In our small cohort study, more patients who received GTX+RT achieved R0 resection and N0 status as compared to FFX+RT. No difference in survival was detected but this may be due to inadequate power or choice of subsequent therapies. Larger prospective studies evaluating GTX+RT as an alternative treatment in the NA setting are warranted. Research Sponsor: None.

Systemic Treatment + RT	R0 resection rate	N0 LN status	mOS (p=0.5)	RFS (p=0.5)	OS in pts with R0 resections (p=0.7)	RFS in pts with R0 resections (p=0.7)
FFX	69.0% (n=29)	52.4% (n=22)	2.71 (n=42)	1.49	2.71 (n=29)	1.63
GTX*	89.7% (n=35)	74.4% (n=29)	3.02 (n=39)	1.55	3.02 (n=35)	2.12

*Hazard ratio of death of 0.81 (0.44-1.50) when compared with FFX (p=0.5).

566   **Poster Session**

A pilot study of liposomal irinotecan plus 5-FU/ LV combined with paricalcitol in patients with advanced pancreatic cancer which progressed on gemcitabine-based therapy.

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Background: 5-FU-based chemotherapy is the standard of care for patients with advanced pancreatic cancer progressed on gemcitabine-based therapy. Based on the NAPOLI-1 study, liposomal irinotecan and 5-FU/LV is currently an FDA-approved regimen in this setting with median progression free survival (mPFS) 3.1 months, median overall survival (mOS) 6.1 months and ORR 16%. In pancreatic cancer mouse models, vitamin D was shown to remodel the desmoplastic stroma and when combined with chemotherapy significantly improved animal survival. **Methods:** We conducted a pilot study in patients with advanced pancreatic cancer progressed on gemcitabine-based therapy treated with 5FU $(2,400mg/m^2)$/LV $(400mg/m^2)$/liposomal irinotecan $(70mg/m^2)$ with paricalcitol in two dose level cohorts: paricalcitol 75mcg IV on day 1 weekly (N = 10, dose level 1) or 7mcg/kg IV on day 1 weekly (N = 10, dose level 2). The primary endpoint was the occurrence of grade 3 and 4 toxicities. Dose-limiting toxicities (DLT) were assessed during cycle 1. Secondary endpoints include objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). **Results:** Between 8/29/2019 to 5/6/2021, a total of 20 patients were enrolled in the study. No DLTs or grade 4 adverse events were observed in either paricalcitol cohort. The most common toxicities were gastrointestinal (nausea, diarrhea), fatigue and anemia and were similar in both cohorts. Only one grade 3 adverse event was possibly due to paricalcitol (spinal fracture). 2/10 patients experienced an objective response, one of which was confirmed. Median follow up was 6.1 months. At the time of analysis, one patient remains on liposomal irinotecan and 5-FU/LV and mPFS of all patients is 3.57 months and mOS is 6.15 months. The mPFS is 3.55 months for dose level 1 and 5.34 months for dose level 2 (p = 0.3). The mOS is 6.15 months for dose level 1 and 6.66 months for dose level 2 (p = 0.4). **Conclusions:** Administration of paricalcitol in combination with liposomal irinotecan and 5-FU/LV is well tolerated in patients with advanced pancreatic cancer, however does not appear to improve response rate or survival outcomes. Correlative analyses are ongoing. Clinical trial information: NCT03883919. Research Sponsor: Ipsen.

567   **Poster Session**

"Super massive" intrahepatic cholangiocarcinoma: Potential role of radiation therapy.

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Background: Intrahepatic cholangiocarcinoma (ICC) is a cancer of the bile ducts within the liver. Most patients have unresectable disease and die of tumor-related liver failure (TRLF); prior data suggest that radiation therapy (RT) may play an important role in decreasing TRLF and improving survival. However, for patients with exceptionally large liver tumors, the role of RT is uncertain. Here, we present our experience using hypofractionated RT for so-called "super-massive" ICC (gross tumor volume > 800cc). **Methods:** We retrospectively collected data from ICC patients treated at the University of Texas MD Anderson Cancer Center. We included inoperable patients (both M0 and M1) who were treated with RT, identified those with a gross tumor volume of 800cc or more (median: 1,300cc IQR: 900-1,900). We analyzed overall survival (OS), local and distant recurrence, tumor-related liver failure (TRLF), and treatment toxicity. **Results:** A total of 12 patients were included. The median age was 60 (IQR: 55-67). The average maximal tumor diameter was 14.1cm (IQR: 12.6-15.8). All but 1 patient received pre-RT systemic therapy. Eight patients (67%) were treated with IMRT, and 4 patients (33%) with proton RT. RT was delivered to a median of 67.5Gy (IQR: 60-73.1) over 15 fractions. At a median follow up of 17.4 months, 5 patients were still alive (2-year OS: 41.7%). Median OS, local recurrence, and distant metastasis from RT were 20.0, 20, and 11.3 months, respectively. Two patients (16.7%) died from TRLF. No grade 2 or higher toxicities were noted. No radiation-induced liver toxicity was present. **Conclusions:** Hypofractionated RT was safe and showed promising clinical outcomes for patients with "super massive" inoperable ICC, compared to historical data. Future studies are still needed to better assess the role of RT in this patient population. Research Sponsor: None.

568 **Poster Session**

Phase II study of SHR-1701 combined with famitinib in the treatment of advanced pancreatic cancer or biliary tract cancer.

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Background: Pancreatic cancer (PC) and biliary tract cancer (BTC) are highly malignant cancers with limited treatment (tx) options. SHR-1701 is a novel bifunctional anti-PD-L1/TGF-βRII agent. Famitinib is a multitargeted tyrosine kinase inhibitor (TKI). Many studies have proved the mutually enhanced effect of anti-angiogenesis and ICI therapy in multiple tumours. Herein, we reported the safety and efficacy of SHR-1701 in combination with famitinib in advanced PC and BTC patients (pts) who have failed previous standard tx. **Methods:** This is an ongoing single-site, exploratory phase II study. PC or BTC pts who have failed ≥1 prior therapy would be enrolled into PC or BTC cohort, and received SHR-1701 plus famitinib until disease progression or unacceptable toxicity. SHR1701 would be intravenously given at a fixed dose of 30mg/kg q3w. Famitinib was initially given at a dose of 20mg/d. Dose reduction of famitinib to 15mg was allowed if it was intolerable. The primary endpoint was objective response rate (ORR) as per RECIST v1.1. Simon's two-stage minimax design was used in this trial. For each cohort, if ≥2 responses are observed among 15 patients in stage I, the study will proceed to full accrual. **Results:** Up to 15 Sep 2021, 15 pts and 9 pts were enrolled in PC and BTC cohorts respectively. The baseline data are shown in the table. Of 15 evaluable pts in PC cohort, one had complete response, one had partial response (PR), 6 pts had stable disease (SD). The ORR and DCR were 13% and 53%, respectively. The first stage of PC cohort had a sufficient response rate to meet full enrollment. Among 8 evaluable pts in BTC cohort, one had PR (tumor shrinkage > 80%), 4 had SD. The ORR and DCR were 13% and 63%, respectively. 22 pts (92%) experienced treatment-related adverse events (TRAEs). The most frequently reported TRAEs (any grade) were proteinuria (58%), hypertension (42%), and blood urine present (42%). The incidence of Grade 3 TRAEs was 33%, among which the most common ones were hypertension (8%), and bilirubin conjugated increased (8%). No grade 4/5 TRAEs were reported. **Conclusions:** SHR-1701 plus famitinib showed encouraging activity with manageable safety in pts with advanced PC or BTC. Enrollment is ongoing and updated data will be presented. Clinical trial information: ChiCTR2000037927. Research Sponsor: None.

Characteristics	PC cohort (n = 15)	BTC cohort (n = 9)
Median age (range), years	62 (50-66)	54 (45-68)
Females, n (%)	6 (40%)	8 (89%)
Median ECOG PS	1	1
Median prior lines of tx (range)	2 (1-4)	1 (1-2)

569 **Poster Session**

Multi-institutional outcomes of patients aged 75 years and older with pancreatic ductal adenocarcinoma treated with ablative 5-fraction stereotactic magnetic resonance image-guided adaptive radiation therapy (SMART).

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Background: Dose escalated radiation therapy (RT) may improve long-term clinical outcomes compared to standard radiation dose for patients with initially inoperable pancreatic ductal adenocarcinoma (PDAC). Favorable outcomes have recently been reported of ablative stereotactic magnetic resonance image-guided adaptive radiation therapy (SMART) delivered in 5 fractions. The appropriateness of ablative SMART inoperable PDAC patients with advanced age (>75 years) is not well understood. **Methods:** A retrospective analysis was performed of inoperable non-metastatic PDAC patients aged 75 year or older treated on a 0.35T-MR Linac at two institutions. Patients were excluded who did not have at least 3 months follow up after SMART. Fiducial markers were not used. Treatment delivery was typically in breath hold. Most (65.3%) were treated to gross disease only without elective coverage. On-table adaptive replanning was performed for each fraction if needed, primarily to account for interfraction anatomic changes and ensure all organ-at-risk (OAR) constraints were met. Treatment response was defined using RECIST 1.1 criteria and CTCAE v5 criteria was used to assess toxicity. **Results:** 49 patients were evaluated with median age of 81 years (range 75-91). ECOG performance status (PS) was 0-1 in 89.8%. PDAC was locally advanced (46.9%), borderline resectable (36.7%), or medically inoperable (16.3%). Median CA19-9 at diagnosis was 235.8 U/mL. Most received induction chemotherapy (83.7%), usually gemcitabine/nab-paclitaxel (63.3%) and rarely FOLFIRINOX (12.2%), for a median 3.2 months. Median prescribed dose was 50 Gy (range, 40-50 Gy). Surgery was performed in 18.4% after a median 10 weeks from SMART, all having negative margins. Median follow-up was 14 months from diagnosis. Median and 1-year local control (LC) was 29 months and 88.9%, respectively. Median and 1-year progression free survival (PFS) was 13 months and 53.8%, respectively. Median and 1-year estimated overall survival (OS) was 23 months and 78.9%, respectively. ECOG PS < 2 was the only significant predictor of improved OS on multivariate analysis with a trend towards significance for induction chemotherapy >3 months. Acute and late grade 3+ toxicity rates were 8.2% and 4.1%, respectively. **Conclusions:** Ablative 5-fraction SMART is associated with encouraging long-term LC and OS among elderly patients with PDAC. This novel treatment strategy is noninvasive, does not require anesthesia, is remarkably well tolerated among patients with advanced age despite the high prescription dose, and therefore should be strongly considered especially among older patients who have limited treatment options. Research Sponsor: None.

570   **Poster Session**

Ciprofloxacin plus gemcitabine-based chemotherapy in patients with metastatic pancreatic ductal adenocarcinoma: A pilot study of microbiome manipulation.

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Background: Gemcitabine-based chemotherapy is an approved therapy for treatment-naïve metastatic pancreatic ductal adenocarcinoma (PDAC). Inherent resistance to gemcitabine inevitably leads to cancer progression and shorter survival. It has been demonstrated that bacteria are a component of the PDAC tumor microenvironment and may play a critical role in mediating resistance to chemotherapy. Hence, the coadministration of an antibiotic to chemotherapy may potentiate antitumour drug responses. We conducted a pilot study to assess the efficacy and safety of ciprofloxacin plus gemcitabine-based chemotherapy in patients with treatment naïve metastatic PDAC. We also aimed to study gut microbiome changes during treatment with ciprofloxacin. **Methods:** This was a single arm study conducted at the National University Cancer Institute, Singapore. Patients (pts) with histologically confirmed metastatic PDAC were treated with nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) on days 1, 8, and 15 every 4 weeks, in combination with oral ciprofloxacin 500 mg twice daily. Treatment was continued until disease progression or intolerable toxicity. DNA extraction, 16S rRNA amplification and sequencing for bacteria were performed on pre- and post-treatment stool samples. Primary endpoint of this study was response rate and safety of the treatment combination. Secondary endpoints included progression free survival (PFS), overall survival (OS) and microbiome changes after treatment with ciprofloxacin. **Results:** From Mar 2019 – Feb 2021, 8 pts were recruited. Median age was 71 years old. Best response was stable disease in 5 (62.5%) pts and 3 pts had progressive disease (PD). Median PFS and OS were 4.3 and 15.4 months, respectively. 2 pts developed grade 4 neutropenia and 1 pt had grade 3 febrile neutropenia. Rash was common with 50% of pts developed grade 1/2 rash. No additional toxicities from ciprofloxacin were observed. Preliminary stool analysis showed significant differences in individual bacterial strains across all timepoints in the PD vs. SD groups. There was also an increased abundance in gammaproteobacteria resistant to ciprofloxacin treatment in pts with PD. **Conclusions:** Gemcitabine-based chemotherapy plus ciprofloxacin demonstrated clinical activity and acceptable safety profile in PDAC. Our study also highlighted that gut microbiome may play a critical role in mediating resistance to chemotherapy. Clinical trial information: NCT04523987. Research Sponsor: National University of Singapore iHealthtech Microbiome in Health, Disease and Ageing Research Grant.

571 Poster Session

Can stereotactic ablative radiotherapy for oligometastatic pancreatic cancer help avoid perpetual chemotherapy and improve outcomes?

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Background: The oligometastatic state is increasing recognized and improved outcomes after local regional therapies have been observed in many malignancies, however there is a paucity of data on outcomes of patients with limited extent pancreatic ductal adenocarcinoma (PDAC). We hypothesize oligometastatic pancreatic cancer (OPanc) with 1-5 metastases would benefit from stereotactic ablative radiotherapy (SABR) to all active sites of disease, can improve outcome, and offer time off chemotherapy. Here in, we report our institutional experience of treating OPanc with SABR to evaluate the outcome and feasibility of the approach and compare outcomes with other institutional cohorts. **Methods:** A retrospective review was conducted on patients with stage IV PDAC who received SABR after noted to have OPanc. Patients with a histological diagnosis of PDAC, number of metastases ranging between 1-5, and who received SABR to all active disease at time of treatment were included. We identified a comparable group of 16 patients with similar metastatic burden but did not receive SABR. Overall survival and time off chemotherapy were evaluated in addition to assessment of each patients' disease course. **Results:** Fourteen patients met the inclusion criteria. Five patients had metastases confined to lung only and nine to the liver only. Median baseline CA 19-9 was 105 U/mL (range < 1, 921 U/mL). Eight patients had metachronous OPanc diagnosis. SABR was delivered to 22 metastatic tumors. Median progression free and overall survivals were 25 and 12.8 months, and 46 and 14.5 months for the SABR treated and the chemotherapy cohorts respectively. A total of 85.7% of patients that received SABR had a chemotherapy treatment break of greater than 6 months. **Conclusions:** Management of OPanc (1-5 lesions) with SABR as local regional therapy could improve outcomes in this selected population and warrants prospective evaluation. Research Sponsor: None.

572

A single-center analysis of 30- and 90-day post-pancreatectomy complications in patients undergoing neoadjuvant radiation with EBRT versus MRI-guided SBRT.

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Background: Stereotactic MRI -guided adaptive radiation therapy (SMART) is being investigated for enhanced efficacy in locally advanced, borderline resectable and medically inoperable pancreatic cancer. Traditionally, conventionally fractioned chemoradiation (EBRT) has been used for operable patients. We sought to evaluate whether there would be differences in surgical complications and outcomes in the 30- and 90- day postoperative period in patients who received either neoadjuvant EBRT or SMART followed by definitive surgery. **Methods:** A retrospective single-center analysis of patients with either resectable, borderline resectable or locally advanced tumors of the pancreas or duodenum, treated with neoadjuvant radiation and surgical management between 2014 and 2021 was performed. Patient demographics and post-surgical complications were collected and stratified according to both treatment arms. The International Study Group of Pancreatic Surgery (ISGPS) classifications were used to define and grade postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postpancreatectomy hemorrhage (PPH). A univariate analysis was done followed by a multivariate analysis. **Results:** Among the 65 patients (mean age 62.6 years, 46% female) who underwent definitive surgical intervention, 44 (67.7%) received EBRT, and 21 (32.3%) received SMART. Baseline characteristics including age, sex, race, ASA, and Charlson comorbidity index (CCI) scores were found to be similar. On univariate analysis, PPH was significantly higher in SMART (OR, 6.6; 95% CI, 1.2 to 37.3; p = 0.034). After adjusting for confounders on multivariate analysis, it appears there is a trend towards higher PPH in the SMART cohort (p = 0.052). **Conclusions:** Neoadjuvant SMART followed by definitive surgery is not associated with worse outcomes in the 30- and 90- day postoperative period vs. neoadjuvant EBRT. Although there was a trend towards PPH on multivariate analysis, further discussion is warranted involving vascular resection, vascular stents and anticoagulation. Research Sponsor: None.

	EBRT (n = 44)	SBRT (n = 21)	p Value
Age	63.2 + 10.2	61.4 + 6.5	0.406
Female sex	21 (47.7%)	9 (42.9%)	0.713
BMI	25.2 + 3.8	27.7 + 5.2	0.031
Operative time (mins)	372 + 103	380 + 50	0.657
EBL (mL)	319 + 227	418 + 272	0.129
Readmission 30 days	7 (15.9%)	1 (4.8%)	0.201
Readmission 90 days	10 (22.7%)	5 (23.8%)	0.923
POPF	4 (9.1%)	0 (0.0%)	0.296
PPH	2 (4.5%)	5 (23.8%)	0.031
DGE	3 (6.8%)	0 (0.0%)	0.545
Length of stay (days)	8.3 + 2.9	8.6 + 4.2	0.799
Resectability			1.000
Resectable	1 (2.3%)	0 (0.0%)	
Borderline	41 (93.2%)	21 (100%)	
Locally advanced	2 (4.5%)	0 (0.0%)	

573 Poster Session

Pathological outcomes of pancreatic adenocarcinoma (PA) after preoperative high biological effective dose (BED) magnetic resonance image-guided radiation therapy (MRgRT).

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Background: Pre-operative radiotherapy (RT) for PA has the potential to reduce positive surgical margin rates and increase pathologic tumor response, which has been associated with improved survival. Increasing the BED can improve local control and overall survival for patients with unresectable PA. Use of stereotactic body radiation therapy (SBRT) to achieve a higher BED has been limited by toxicity to adjacent radiosensitive structures, but this can be mitigated by MRgRT. We describe our use of MRgRT prior to potentially curative resection of localized PA. **Methods:** We performed a single institution retrospective analysis of all patients with localized PA who received high BED SBRT on the MR Linac followed by surgical resection with curative intent. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events, version 5.0. Tumor response was evaluated according to the College of American Pathologists tumor regression grading criteria (CAP-TRG), ranging from CAP 0 indicating pathologic complete response to CAP grade 3 indicating no response. Ordinal logistic regression model was used to assess the association between time from RT to surgery and TRG. Follow up included MRI or CT scans at least every three months. **Results:** We analyzed 26 patients with borderline resectable (80.8%), locally advanced (11.5%), and resectable (7.7%) tumors who received high BED MRgRT followed by surgical resection. Median age at diagnosis was 68 years (34 - 86). Most patients received chemotherapy (80.8%) prior to RT, with 81% of these receiving FOLFINIRNOX and 19% receiving gemcitabine/nab-paclitaxel. All patients received MR-guided high BED SBRT to a median dose of 50 Gy (40 - 50) in 5 fractions. On-table adaptive replanning was performed in 88% of patients, with 74% having all 5 fractions adapted. No acute grade 2+ toxicity associated with RT was observed. The median time to resection was 50 days (37 – 115), and the procedure types included: Whipple (69%), distal (23%), or total pancreatectomy (8%). The R0 resection rate was 96% and no perioperative deaths occurred within 90 days. Complete (0) or near-complete (1) pathologic response was observed in 35% of cases and the time from RT to surgery was positively associated with TRG (R^2= 0.22, p = 0.0003). The median follow-up after RT was 16.5 months (3.9- 26.2) during which 9 patients recurred, and 3 patients died of disease. The derived median progression-free survival from RT was 13.2 months. **Conclusions:** These initial pathology outcomes following high BED MR-guided SBRT are encouraging and suggest that the time from SBRT to surgical resection is associated with response. This finding is consistent with results from other preoperative GI tumor sites and results from prospective studies using high BED SBRT with MRI guidance in combined modality therapy against PA are eagerly awaited. Research Sponsor: None.

574 Poster Session

A phase Ib study of guadecitabine and durvalumab in patients with advanced hepatocellular carcinoma, pancreatic adenocarcinoma, and biliary cancers.

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Background: Pancreatic (PC) and biliary cancers (BC) are cold tumors with limited activity of single agent immune checkpoint inhibitors. DNA methyltransferase inhibitors (DNMTi) have immunomodulatory effects manifested by upregulation of interferon pathways and expression of endogenous retroviral signatures. We performed a phase Ib study of the DNMTi guadecitabine (G) and durvalumab (D) in patients (pts) with hepatocellular carcinoma, PC and BC. We report initial results from the PC and BC cohorts. **Methods:** This is a phase Ib study to establish the maximum tolerated dose (MTD) of the combination (dose escalation; 3+3 design) and evaluate the objective response rate (ORR) in expansion cohorts of PC and BC. G was given at escalating doses of 30 mg/m2 and 45 mg/m2 subQ for 5 days q 28 days. D was given at 1500 mg IV on day 8 of each cycle. Expansion was started at the MTD. Eligibility criteria included ECOG 0-1, ANC ≥ 1,500, platelets > 100,000, albumin ≥ 2.5 g/dL, total bilirubin ≤ 2.5 x upper limit of normal, failure of ≥ 1 prior line of therapy for advanced disease. Prior anti PD-1/PDL-1 was not allowed. Tumor biopsies were performed during screening and on cycle 3 day 1. **Results:** A total of 11 pts were treated in dose escalation; 3 at dose level 1, and 8 (6 evaluable for DLT) at dose level 2. Given lack of dose-limiting toxicities, MTD was the highest planned dose of G at 45 mg/m2. 24 pts with PC and 23 pts with BC were treated in dose escalation and expansion. For the PC cohort: median age was 66 (43, 93), 29% female, 67% ECOG 1, and median number of prior therapies 2 (1,3). For the BC cohort: median age was 61 (41, 85), 52% female, 78% ECOG 1, and median number of prior therapies 1 (1,3). All grade treatment related AEs in ≥10% of pts were neutropenia (55%), leukopenia (50%), anemia (33%), fatigue (33%), thrombocytopenia (17%), nausea (15%), and anorexia (10%). Grade 3/4 AEs in ≥10% of pts were neutropenia (40%), leukopenia (35%), and anemia (13%). There was 1(5%) PR in PC cohort lasting > 24 mo and ongoing and 1(5%) in BC cohort lasting 12 mo; both were in MSS pts. SD was noted in 7/24 (29%) PC and 5/23 (22%) BC pts, 8 of which lasted ≥4 mo. Median PFS for PC and BC was 2.1 mo [1.9, 3.8] and 1.9 mo [1.4, 2] respectively. Median OS for PC and BC was 4.4 mo [3.4, NR] and 8.6 mo [6.4, NR]. Six and 12 mo OS rates are 38% [21, 66] and 27% [13, 56] for PC; 69% [52, 91] and 35% [19, 63] for BC. 4% of PC pts and 42% of BC pts received another therapy after progression. **Conclusions:** The combination of G and D has a manageable safety profile in pts with advanced PC and BC; grade 3/4 AEs were limited to myelosuppression. The combination had limited clinical activity based on ORR and PFS in this unselected, pretreated population; however, a subset of pts appeared to derive prolonged clinical benefit, and OS rates were comparable to standard second line chemotherapy, despite a minority of pts receiving subsequent treatment. Biomarker analyses are ongoing. Clinical trial information: NCT03257761. Research Sponsor: Stand Up to Cancer (SU2C)/Van Endel Research Institute Epigenetics Dream Team, Pharmaceutical/Biotech Company.

575 **Poster Session**

Efficacy of SBP-101, a polyamine metabolic inhibitor, administered in combination with gemcitabine and nab-paclitaxel, as a first-line treatment for patients with metastatic pancreatic ductal adenocarcinoma.

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Background: SBP-101, a polyamine metabolic inhibitor, inhibited growth in 6 human pancreatic ductal adenocarcinoma (PDA) cell lines and 3 murine xenograft tumor models of human PDA. SBP-101 monotherapy in heavily pre-treated PDA patients ($>$ 2 prior regimens) showed a median survival of 5.9 months at the optimal dose level. Purpose: To assess the PK, safety and efficacy of SBP-101 in combination with gemcitabine (G) and nab-paclitaxel (A) in patients with previously untreated metastatic PDA. **Methods:** In a modified 3+3 dose escalation scheme, subcutaneous injections of SBP-101 were dosed at 0.2, 0.4 or 0.6 mg/kg days 1-5 of each 28-day cycle. G (1000 mg/m^2) and A (125 mg/m^2) were administered intravenously on Days 1, 8, and 15 of each cycle. PK was evaluated on day 1 of cycle 1 in cohorts 1-3. Safety was evaluated by clinical and laboratory assessments. Efficacy was assessed by CA19-9 levels, objective response using RECIST criteria, progression-free survival (PFS) and overall survival (OS). A 4th cohort using a modified dosing schedule of 0.4 mg/kg SBP-101 days 1-5 for cycles 1-2 and days 1, 8, and 15 every cycle thereafter was added to mitigate hepatic toxicity, and that dose and schedule were recommended for Phase 1b expansion. **Results:** Fifty patients were enrolled (N=25, Phase 1a and N=25, Phase 1b) and received up to 13 treatment cycles. SBP-101 plasma C_{max} and AUC_{0-t} increased in a slightly more than dose proportional manner and were unchanged by the addition of G and A. PK parameters of G and A were unaltered by increasing doses of SBP-101. The most common nonserious adverse events related to SBP-101 ($>$10%) are fatigue (N=14), LFT/transaminase abnormalities (N=15), vision abnormalities (N=10), injection site pain (N=13), dehydration (N=7), nausea (N=7). Serious adverse events related to SBP-101 observed in some subjects include hepatic toxicity (N=6) and retinal toxicity (N=8) both occurring after prolonged treatment and requiring dose reduction or discontinuation. At the recommended dose and schedule (N=30), CA19-9 levels decreased 60-99% in 19 of 29 evaluable patients, with 1/29 (3%) achieving a complete remission 13/29 achieving partial responses (45%) and 10/29 achieving stable disease at 8 weeks (35%). PFS was confounded by SBP-101 dosing holds implemented to investigate potential toxicity. Sixteen subjects are in survival follow-up. Median OS is 10.1 months and is not final. **Conclusions:** Interim results suggest SBP-101 may enhance first-line treatment with G and A in patients with metastatic PDA. Hepatic toxicity can be mitigated with dose reduction or discontinuation. A vision screening program will be used in future studies to mitigate retinal toxicity. Clinical trial information: NCT03412799. Research Sponsor: Panbela Therapeutics, Inc.

Phase II study of PEGPH20 plus pembrolizumab for patients (pts) with hyaluronan (HA)-high refractory metastatic pancreatic adenocarcinoma (mPC): PCRT16-001.

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Background: Stromal HA poses a physical barrier and protects tumor cells from immune surveillance. PEGPH20 is a pegylated, human recombinant PH20 hyaluronidase that remodels tumor stroma. Preclinical studies of PEGPH20 showed improved infiltration of cytotoxic T-lymphocytes and delivery of chemotherapy and PD1/PD-L1 antibodies. This study aimed to evaluate the efficacy, safety, and translational biomarkers of PEGPH20 plus pembrolizumab in pts with HA-high refractory mPC. **Methods:** mPC pts with HA-high expression, ECOG PS 0-1, $\leq$ 2 prior therapies for metastatic disease, life expectancy $\geq$ 12 weeks were treated with PEGPH20 3 μg/kg iv on D1, D8, D15 and pembrolizumab 200 mg iv on D1 in 21-day cycles. Primary endpoint was progression-free survival (PFS). Secondary endpoints were safety, overall survival (OS), and objective response rate (ORR). Blood and tumor biopsies were collected at baseline and on-study. Translational endpoints included flow cytometry and IHC for immune subsets, T-cell receptor sequencing, immune transcriptome, circulating cytokines, and plasma and tumor HA levels. Assuming a one-sided α-level of 0.05 and power of 80%, 31 evaluable pts were needed to detect an improvement of median PFS from 3 to 6 months. **Results:** Between May 2019 to Nov 2019, 38 pts were screened for HA expression, and 8 pts were enrolled, with median age 68 years (range 60-73), 7 males, and median 2 prior therapies (range 1-4). The accrual was stopped early by Halozyme Pharmaceuticals due to lack of benefit from PEGPH20 added to chemotherapy in the HALO-301 study. Treatment exposure median was 2 cycles (range 1-6). Reasons for study discontinuation were disease progression (n = 4), termination by sponsor (n = 3), patient withdrawal to enroll in hospice (n = 1). Treatment related toxicities were musculoskeletal (n = 6, grade 1/2), edema (n = 2, grade 1), fatigue (n = 1, grade 3), dyspnea (n = 1, grade 2), hypothyroidism (n = 1, grade 2). Median OS was 7.2 months (95% CI 1.2-11.8), and median PFS was 1.5 months (95% CI 0.9-4.4). Best response was stable disease (n = 2, 25%) lasting 2.2 and 9 months, respectively, and no responses were noted. Patients with available molecular sequencing data had MSS tumors. Translational biomarkers will be presented. **Conclusions:** Pembrolizumab and PEGPH20 did not increase PFS compared to historical data among heavily pretreated mPC pts, but the median OS of 7.2 months is encouraging. Translational analyses will provide insights into immune modulatory effects from PEGPH20 that could inform future studies with stroma targeted therapies and immune checkpoint blockade in mPC. Clinical trial information: NCT03634332. Research Sponsor: Merck, Pharmaceutical/Biotech Company.

577

Prognostic factors associated with survival in patients with pancreatic cancer treated on early phase immune-checkpoint inhibitor clinical trials.

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Background: Immune-checkpoint inhibitors (ICI) have altered the treatment landscape of various solid tumors, but clinical outcomes in patients with pancreatic ductal adenocarcinoma (PDAC) continue to remain dismal. Data are needed to determine prognostic factors of survival to ICI-therapies in pancreatic cancer to better inform future recruitment in immunotherapy-based early clinical trials. **Methods:** This is a single center, retrospective analysis of patients with PDAC treated with ICI-based therapy as part of phase I trials at MD Anderson Cancer Center. Patients enrolled in a phase I study and treated between 2014 to 2021 were included in the analysis. Descriptive analysis included patient characteristics, progression free survival (PFS) and overall survival (OS). Cox proportional hazards were used to assess associations between patient or tumor characteristics and survival endpoints. **Results:** One hundred and twenty-two patients were included in this study and received a median of two prior lines of therapy (IQR 1-3). The most commonly utilized ICI were PD-L1 inhibitors (56%) and PD-1 inhibitors (34%). Most patients (96%) received ICI in combination with another investigational agent and 9% of patients received ICI in combination with chemotherapy. The median duration of treatment was 1.38 months (IQR 0.69-2.56). The median PFS was 1.81 months (95% CI 1.78-2.04) and the median OS was 4.83 months (95% CI 4.08-5.92). Univariate analysis showed improved PFS in patients with an albumin of ≥3.5 (1.94 vs 1.32 months, HR 0.29, 95% CI 0.14-0.60, p = 0.001) and Hgb ≥10.5 (1.87 vs 1.81 months, HR 0.63, 95% CI 0.4-0.98, p = 0.039); a longer OS was demonstrated in patients who had lung only metastases (7.92 vs. 4.18 months, HR 0.4, 95% CI 0.21-0.76, p = 0.006), albumin ≥3.5 (5.52 vs. 1.68 months, HR 0.4, 95% CI 0.2-0.8, p = 0.010), and a Hgb ≥10.5 (5.29 vs 4.11 months, HR 0.59, 95% CI 0.38-0.93, p = 0.022). Patients with an ANC/ALC ratio of ≥5 had a shorter OS compared to patients with an ANC/ALC ratio of < 5 (3.98 vs 6.54 months, HR 1.78, 95% CI 1.17-2.69, p = 0.007). Multivariate analysis showed that an albumin ≥3.5 predicted improved PFS (HR 0.41, 95% CI 0.19-0.90, p = 0.026) and an ANC/ALC ratio of ≥5 predicted shorter OS (HR 2.59, 95% CI 1.59-4.19, p < 0.001). **Conclusions:** Results of this large, single center retrospective study demonstrate that most patients with PDAC treated with ICI based therapies as a part of early phase clinical trials experience disease progression shortly after initiation of therapy and have a limited overall survival. Pretreatment albumin ≥3.5 predicted improved PFS and ANC/ALC ratio ≥5 predicted shorter OS. Research Sponsor: None.

578 Poster Session

Phase 2 study of 9-ING-41, a small molecule selective glycogen synthase kinase-3 beta (GSK-3β) inhibitor, with gemcitabine/nab-paclitaxel (GnP) in first-line advanced pancreatic ductal adenocarcinoma (PDAC).

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Background: GSK-3β overexpression is associated with worse prognosis and chemotherapy resistance in PDAC. GSK-3β inhibition reverses chemotherapy-resistance by inhibiting chemotherapy-induced, ATR-mediated, DNA damage response. 9-ING-41 has significant anti-tumor activity through apoptosis induction, anti-fibrotic activity and NK/T-cell effector stimulation. We hypothesized that 9-ING-41 in combination with GnP chemotherapy would lead to anti-tumor activity, with improved tumor responses in patients with advanced PDAC in the first line setting. **Methods:** Primary endpoint is disease control rate (DCR). DCR = confirmed complete response (CR), partial response (PR), or stable disease (SD) $\geq$ 16 weeks (wks). Secondary endpoints are safety and ORR (overall response rates). Eligibility: Advanced PDAC, ECOG PS 0-2, no prior therapy in the metastatic setting and no systemic therapy in prior 6 months. Pts received 9-ING-41 15mg/kg IV twice-weekly with G 1,000 mg/m^2 and nP 125 mg/m^2 on days 1,8,15 of a 28-day cycle. Simon 2-Stage Design for DCR of 65% and null hypothesis of 50% (historical control), 80% power and 2 sided-significance level of.05. Up to 23 fully evaluable pts planned for stage 1 and if $\geq$ 12 evaluable patients achieve a DCR 37 additional pts will be enrolled on a second stage or a randomized study commenced. **Results:** As of Sept 27, 2021, 42 pts enrolled. Median age: 67. 24 females, 18 males. 38 pts with metastatic and 4 with locally advanced disease. Prior adjuvant therapy: 4 pts each FOLFIRINOX and gemcitabine-based. No 9-ING-41-attributable SAEs to date. 9-ING-41 attributed AEs: visual disturbance: 24 (75%) G1/2, 1 (3%) G3; infusion reactions 9 (28%) G1/2. Chemotherapy-related AEs: anemia 13 (40%) G1/2, 1 (3%) G3; neutropenia 2 (6%) G1/2, 13 (40%) G3/4; thrombocytopenia 9 (28%) G1/2, 2 (6%) G3/4; diarrhea 8 (25%) G1/2, 4 (13%) G3; fatigue 9 (28%) G1/2, 3 (9%) G3; nausea/vomiting 24 (75%) G1/2, 1 (3%) G3; constipation 9 (28%) G1/2; febrile neutropenia 5 (16%) G3/4. In 21 pts currently evaluable for response, DCR was 62% and ORR 43%. There were 2 confirmed CRs, 6 confirmed and 1 unconfirmed PRs, 4 SD and 8 disease progressions were observed. Amongst responder's median duration of response has not yet been reached. **Conclusions:** 9-ING-41 plus GnP demonstrated encouraging clinical activity but chemotherapy-related AEs were significant. Based on efficacy data to date, including confirmed CRs, we have commenced a randomized phase 2 study, evaluating 9-ING-41 plus GnP vs Gn P alone. Enrollment to the randomized study is now open (NCT03678883). Clinical trial information: NCT03678883. Research Sponsor: Arcuate.

579 Poster Session

Understanding extended duration of therapy (DOT) among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens.

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Background: Few analyses have identified characteristics associated with extended DOT (eDOT) among a large group of patients (pts) treated with liposomal irinotecan. This study examines the characteristics associated with eDOT among pts with mPDAC treated with liposomal irinotecan in a real-world setting. **Methods:** This retrospective observational study utilized the Flatiron Health EHR database from over 280 cancer clinics in the US. Data were analyzed for adult pts with mPDAC treated with liposomal irinotecan-based regimens between January 2016 and October 2020. eDOT was defined as a DOT > 2 standard deviations (SD) above the mean. Demographic and clinical characteristics evaluated included age, sex, stage at diagnosis, ECOG performance score (PS), and the number of prior lines of therapy at the time of treatment initiation. Dose delays and dose reductions during treatment were assessed. Additionally, changes in lymphocyte counts during treatment were described. Chi-squared test and Fisher's exact test were used to test for significance for categorical variables and the t-test was used for continuous variables. **Results:** 675 pts with mPDAC treated with a liposomal irinotecan-based regimen were included. The overall mean DOT was 14.6 weeks (SD: 22.1). There were 30 pts (4.4%) that met the definition for eDOT. Patient sex and median age at treatment initiation were similar between those with eDOT and non-eDOT: male, 46.7% vs. 51.9% (p = 0.582); age, median 70 years vs 69 years (p = 0.923), respectively. A higher proportion of pts with eDOT had ECOG PS of 0-1 compared to those with non-eDOT, 73.3% vs 57.7%, respectively (p = 0.397). At treatment initiation 80.0% of pts who had eDOT had a serum albumin level of $\geq$ 35g/L versus 55.2% of pts with non-eDOT (p = 0.013). On average, those with eDOT experienced a 55.1% reduction in lymphocyte count (baseline to nadir) during treatment compared to a 34.7% reduction among pts with non-eDOT (p < 0.0001). Pts who experienced eDOT were more likely to be treated in earlier lines of therapy than those with non-eDOT: 33.3% vs 14.1% received 0 prior lines and 46.7% vs 47.3% received 1 prior line, respectively (p = 0.008). 53.3% of pts with eDOT experienced a dose reduction (of at least 7mg/m^2) compared to 24.7% pts with non-eDOT (p = 0.0005). All pts with eDOT experienced a dose delay of > 16 days during treatment versus 45.3% of pts with non-eDOT (p < 0.0001). **Conclusions:** This real-world study identified pts treated earlier in their disease course with a liposomal irinotecan-based regimen and normal baseline serum albumin were more likely experience extended DOT. Treatment modifications and delays appear to have enabled longer treatment duration with liposomal irinotecan-based regimens. Further prospective studies should be considered to characterize factors that may predict extended DOT. Research Sponsor: Ipsen.

580 **Poster Session**

Real-world clinical outcomes of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens: Impact of prior irinotecan (IRI) exposure.

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Background: Subgroup analyses of the NAPOLI-1 study identified that among patients who were IRI naïve prior to entering the clinical trial, a survival benefit was observed between the study arm and control arm (overall survival (OS): 6.7 months vs 4.2 months). This treatment benefit was not observed among those previously exposed to IRI (OS: 4.6 months in study arm vs 4.8 months in control arm). This study sought to understand the impact of prior exposure to IRI on clinical outcomes among patients treated with liposomal irinotecan in the real-world setting. **Methods:** This retrospective observational study utilized the Flatiron Health EHR database. Data were analyzed for adult patients with mPDAC treated with liposomal irinotecan -based regimens between January 2016 and October 2020. Patient characteristics, OS and progression-free survival (PFS) were assessed. Prior IRI was defined as IRI given in a prior regimen in the metastatic setting. Cox proportional hazard (PH) methods were used to calculate hazard ratios (HRs). HRs were adjusted to account for demographics and relevant clinical covariates. Patients without prior exposure to IRI were used as the reference population for the Cox PH model (an HR < 1 represents worse survival for unexposed patients relative to the exposed). **Results:** 675 patients with mPDAC treated with a liposomal irinotecan-based regimen were included. Median age at treatment initiation was 69 (IQR: 62 – 75) years and among patients with available ECOG performance status (PS), 77.4% had a PS of 0-1. 181 (27%) patients were previously exposed to IRI in the metastatic setting (Table). The unadjusted OS HR was 1.3 (95% CI: 1.1 – 1.6, p < 0.001) and the unadjusted PFS HR was 1.4 (95%CI: 1.2 – 1.7, p < 0.001). After adjustment for baseline characteristics the adjusted OS HR was 1.0 (95% CI: 0.8 – 1.3, p = 0.8836) and the adjusted PFS HR was 1.1 (95%: 0.8 – 1.4, p = 0.5626). **Conclusions:** The results of this study suggest prior exposure to IRI is not a predictor of worse clinical outcomes for patients treated with liposomal irinotecan-based treatment when accounting for key clinical characteristics in a multivariable model. The results from this real-world study can be used to support treatment sequencing decisions for patients with mPDAC following first line therapy. This is the largest real-world evidence study to date of patients with mPDAC treated with liposomal irinotecan. Research Sponsor: Ipsen.

	Overall Cohort, N = 675	Prior IRI exposure, N = 181	No Prior IRI Exposure, N = 494
Age at index, median (IQR)	69 (62 - 75)	65 (59 - 71)	71 (63 - 76)
Male, n (%)	349 (52%)	94 (52%)	255 (52%)
ECOG PS, n (%)			
0 - 1	394 (77%)	106 (79%)	288 (77%)
2+	115 (23%)	28 (21%)	87 (23%)
Missing	166	47	119
Prior lines of therapy, n (%)			
0	101 (15%)	0 (0%)	101 (20%)
1	319 (47%)	28 (15%)	291 (59%)
2+	255 (38%)	153 (85%)	102 (21%)
Prior progression, n (%)	540 (80%)	170 (94%)	370 (75%)

581 Poster Session

A phase I dose-escalation study of eryaspase in combination with modified FOLFIRINOX in locally advanced and metastatic pancreatic ductal adenocarcinoma: Interim update.

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Background: The prognosis for advanced metastatic pancreatic adenocarcinoma remains dismal with median survival of 12-15 months in most recent trials, highlighting the urgent need for novel therapeutic agents. mFOLFIRINOX remains the standard of care for the first line treatment of advanced disease, with historical objective response rate (ORR) of ~31%. Eryaspase, L-asparaginase (ASPNase) encapsulated in red blood cells (RBCs), is an investigational product under development. Following infusion, asparagine is actively transported in RBCs where it is hydrolyzed by encapsulated ASPNase. The reduction in plasma concentration of this essential amino acid leads to cancer cell death. A second line pivotal randomized phase III trial (Trybeca-1), which compares chemotherapy (Gemcitabine + Nab-Paclitaxel or 5-Fluorouracil + Irinotecan) with or without Eryaspase, has completed enrollment with results pending (NCT03665441). **Methods:** Patients with locally advanced or metastatic biopsy-proven pancreatic adenocarcinoma were treated with the combination of mFOLFIRINOX plus Eryaspase. The design was a standard 3 +3 dose escalation. mFOLFIRINOX was given as 5-Fluorouracil 2400 mg/m2 over 46 hours, Oxaliplatin 85 mg/m2, Irinotecan 150 mg/m2 plus Eryaspase 75 units/kg at dose level 0 or 100 units/kg at dose level 1. Key eligibility criteria include performance status of 0 or 1, locally advanced or metastatic disease, and adequate organ function. The primary objectives were to determine the maximum tolerated dose (MTD) and to determine the safety of this combination. **Results:** To date, nine patients have been enrolled with a mean age of 70. Four patients had locally advanced disease and five had metastatic disease. Three patients were enrolled at dose level 0 and six at dose level 1, with no dose limiting toxicities (DLT). Eight patients have had imaging to evaluate response: the ORR was 50% with four partial responses (PRs); 50% (N = 4) had stable disease (SD); disease control rate (PR + SD) was 100%. There were no grade 4 adverse events (AEs). The most common grade 3 AEs were hypokalemia (33%), fatigue (11%), and hypotension (11%); but they were beyond the DLT period of 28 days. The most common grade 1/2 AEs were neuropathy (78%), elevated liver enzymes (78%), nausea (78%), anemia (66%), fatigue (66%), diarrhea (66%), and mucositis (44%). **Conclusions:** The novel combination of mFOLFIRINOX plus Eryaspase was well tolerated with no DLT and has encouraging signs of clinical activity. The MTD has been declared with 5-FU 2400 mg/2, Oxaliplatin 85 mg/2, Irinotecan 150 mg/m2, and Eryaspase 100 units/kg. We plan to expand enrollment to further look at efficacy and are in the process of designing a larger randomized study in the first line setting pending results from the Trybeca-1 trial. Clinical trial information: NCT04292743. Research Sponsor: Erytech.

582   **Poster Session**

Promising survival and disease control in third-line or greater metastatic or locally advanced pancreatic cancer patients following chemo-radiation and novel combination of aldoxorubicin, N-803 IL-15 superagonist, and PDL1- NK cell therapy.

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Background: Pancreatic cancer claimed an estimated 47,050 lives in the USA in 2020, with an expected median overall survival (OS) of 3 months in 3rd line. (Manax ASCO GI 2019), with no evidence of disease control in these late stage patients. We hypothesize that effective response against pancreatic cancer requires orchestration of both the innate and adaptive immune system to accomplish immunogenic cell death with survival benefit. Herein we report the first results of a novel combination immunotherapy protocol of low-dose chemoradiation, cytokine-induced NK and T cell activation via N-803 (an IL-15 cytokine superagonist), and allogeneic off-the-shelf PDL1-targeted high-affinity NK cell (PDL1 t-haNK) infusion. **Methods:** We report data from a multi-center study, on 55 3rd line or greater, subjects treated with low dose, chemo radiation Nab-paclitaxel (100 mg/ m2 IV), Gemcitabine (600 mg/m2 IV); Cyclophosphamide (50 mg PO BID) and low dose SBRT. This induction immuno-modulation therapy to induce DAMPs was followed with investigational agents activating the innate and adaptive systems: Aldoxorubicin (150 mg/m2 IV), N-803, an IL-15 superagonist (15 μg/kg SC) and PD-L1 t-haNK (~2 $\times$ 109cells/dose IV). Prophylactic G-CSF or EPO was not allowed. All treatments were administered on an outpatient basis. **Results:** As of submission, median follow-up is 3.9 months. Median age 62, M:F ratio 35:20. ECOG 0-1,92%. 41/55 (75%) subjects reported a grade $\geq$3 AE related to the chemo radiation, anemia 44%, neutropenia 24%, thrombocytopenia 11%, all others < 10%. SAEs attributed to investigational agents were reported in 5/55 (9%) patients. Of the 44 patients evaluable at 3 months to date, the OS is 81.8% (36/44), 95% CI: 67.3%, 91.8%. The disease control rate of 47 evaluable patients is 36.2% (17/47) 95% CI 22.7%,51.5%. No treatment related deaths have occurred. Treatment is ongoing for 16 subjects, with 14 months as the longest duration on therapy to date. Median OS not yet reached with 28/55 alive to date. Median PFS is 2.4 months (95% CI: 2.0, 3.7) and 36% of subjects not having progressed to date. **Conclusions:** Historical 3 month median OS in 3rd line metastatic pancreatic cancer patients has been exceeded. Early safety and promising efficacy is seen in QUILT 88 investigating a novel combination immunotherapy protocol of low-dose chemoradiation, N-803 and PDL1 t-haNK therapy. Updated data will be presented. Clinical trial information: NCT04390399. Research Sponsor: ImmunityBio.

Palliative radiosurgery for localized pancreatic cancer in the elderly.

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Background: At least 15% of patients diagnosed with localized pancreatic cancer are medically unfit for surgical resection or systemic therapy. Traditionally, these patients are enrolled in palliative care with symptom management alone. With local progression of their disease, they may experience pain, obstruction, weight loss and nausea. Radiosurgery is a localized high dose conformal therapy allowing for noninvasive treatment of pancreatic cancer. This study retrospectively examines the role of palliative radiosurgery as monotherapy for elderly patients who are not candidates for standard of care therapy. **Methods:** From 2017-2021, 28 patients over the age of 80 with biopsy confirmed pancreatic adenocarcinoma and localized disease by imaging were retrospectively evaluated. All had been deemed not to be candidates for surgical resection or systemic chemotherapy. Outcomes were reviewed to evaluate patient characteristics, local control, quality of life, ECOG status and survival duration. **Results:** Median patient age was 84 years (range 80-99). All 28 patients received SBRT radiosurgery to the pancreas with 35-40Gy in 5 fractions with photon LINAC platform. Mean ECOG score was 1.2 at time of treatment. At 6 month follow up, 18 patients were alive with a mean ECOG of 1.4. Four patients reported grade 2 acute GI toxicity in the first three months with no late toxicity reported. Eight patients developed local progression while fourteen patients developed distant metastatic disease. Six patients at least one year out from treatment have no evidence of disease progression. Median overall survival is 10.8 months. **Conclusions:** Pancreatic radiosurgery is a safe and effective method of palliative therapy for elderly patients who are not candidates for surgical resection or systemic therapy. It can provide durable local control, relief of pain and obstructive symptoms, is well tolerated with minimal toxicity and provides favorable survival when compared to palliative care alone. Research Sponsor: None.

584   **Poster Session**

Impact of nuclear factor of activated T cells (NFAT) families as a poor prognostic factor in pancreatic cancer patients.

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Background: Pancreatic cancer microenvironment is crucial in cancer development, and cancer-stromal interactions have been recognized as important targets for cancer therapy. Nuclear factor of activated T-cells (NFAT) has been found in T cells as a transcriptional activator of IL-2, and known to be involved in various processes including the immune system. In cancer tissues, NFAT has been reported to be involved in metastasis. In breast and colorectal cancers, NFATc2 and NFAT5 have been reported to interact with integrins to promote cancer cell migration. On the other hand, in pancreatic cancer, NFAT5 has been reported to be a poor prognostic factor via regulation of PGK1 transcription. In the present study, we evaluated the expression of NFATc2 and NFAT5 in pancreatic cancer and examined their relationship with prognosis. **Methods:** One hundred and sixty five pancreatic cancer patients who underwent curative-intrent resection at our hospital between 2010 and 2020 were included in this study. We performed immunostaining for NFATc2 and NFAT5 using the tissue micro array. We evaluated the expression of NFATc2 and NFAT5 protein and examined their correlation with clinicopathological factors. **Results:** Of the 165 pancreatic cancer cases, we detected increased NFATc2 protein expression in cytoplasm of cancer cells in 53 cases (32.1%) and NFAT5 in 104 cases (63.0%), and NFATc2/NFAT5 co-expression in 43 cases (26.1%). NFATc2 expression was not correlated with any clinicopathological factors, NFAT5 expression was correlated with venous invasion ($p = 0.047$), and NFATc2/NFAT5 co-expression was slightly correlated with Stage ($p = 0.054$). Relapse free survival (RFS) was estimated in all 165 patients. There was no significant difference for RFS in either NFATc2-high group or NFAT5-high group ($p = 0.314$ or $p = 0.574$), however, NFATc2/NFAT5 co-expression group showed significantly poor RFS ($p = 0.023$). Overall survival (OS) was also estimated in all 165 patients. There was no significant difference for OS in either NFATc2-high group or NFAT5-high group ($p = 0.146$ or $p = 0.529$), however, NFATc2/NFAT5 co-expression group showed significantly poor survival ($p = 0.006$). In multivariate analysis, lymphatic invasion, curability and NFATc2/NFAT5 co-expression were independent prognostic factors for RFS, and lymphatic invasion, curability, presence of adjuvant therapy and NFATc2/NFAT5 co-expression were independent prognostic factors for OS. **Conclusions:** In pancreatic cancer, NFATc2/NFAT5 co-expression was suggested to be involved in the critical process of pancreatic cancer progression, and may be a novel therapeutic target. Research Sponsor: None.

585   **Poster Session**

Oral SM-88 plus MPS, an effective yet less toxic treatment option in second-line advanced pancreatic cancer? Final phase II/III study results.

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Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has a poor prognosis in refractory patients (pts). SM-88 Regimen, which comprises oral SM-88 (racemetyrosine, TYME Inc) plus 10mg methoxsalen, 50mg phenytoin, and 0.5mg sirolimus (MPS), has previously shown clinical activity in mPDAC. **Methods:** We report on the final results (primary objective, ORR) of our multicenter, prospective open-label phase II/III RCT (TYME-88-Panc Part 1, NCT03512756) of SM-88 Regimen in pts with mPDAC who had received at least one prior line of therapy. Subjects received either 230 mg BID or 460 mg BID PO SM-88; oral MPS QD was given at the same dose in both arms. **Results:** The last subject was enrolled on Mar 12, 2019. As of Sep 1, 2021, 49 subjects were randomized to either 460 (n = 26) or 920mg (n = 23) SM-88 plus MPS daily (ITT population); 37 were deemed evaluable after completing at least one 28-day cycle of treatment (min 23 days on treatment). The study population was heterogeneous: a majority (32/37 = 86.5%) had failed at least 2 prior lines of chemotherapy. Twenty pts (54.1%) had received FOLFIRINOX in the first line and 16 pts (43.2%), a gemcitabine-based regimen. For evaluable pts, the overall disease control rate (DCR) was 27.0%: 10/37 subjects reached RECIST v1.1-verified stable disease (SD); 3 of the 10 had RECIST-confirmed SD. For the 49 ITT pts, mOS was 3.4 months (mo). For the 37 evaluable pts, mOS was 3.9 mo, and mPFS was 1.9 mo. mOS, mPFS, and DCR did not differ significantly by SM-88 dose. mOS and mPFS trended toward improvement in subjects with fewer prior lines of treatment: for pts in the second line (n = 5), mOS was 8.1 mo (95% CI: 3.0 – no UL), and mPFS was 3.8 mo (95% CI: 0.9 – no UL). Although not confirmatory, exploratory analyses showed that circulating tumor cells decreased on SM-88 Regimen. SM-88 Regimen was well tolerated: only one pt of the 48 ever dosed (2.1%) experienced related SAEs on treatment (Grade 3 abdominal pain, Grade 4 hypotension), which were eventually resolved. Enrollment criteria specified ECOG < = 2 at study entry; these scores were maintained or improved for most pts (24/37 = 64.9%) while on treatment. Overall health and quality of life (QOL) scores via EORTC QLQ-C30 were maintained, trending toward superiority for pts on 920 mg vs. 460 mg (p = ns). **Conclusions:** This final analysis confirmed that SM-88 Regimen was well tolerated, with pts attaining an overall DCR of 27%. Of note, for the small subset of pts treated in the second line, the mOS and mPFS were on par with results achieved in other published randomized PhIII second-line trials for mPDAC. Moreover, SM-88 Regimen exhibited far fewer Grade 3 and 4 AEs than other commonly used cytotoxic regimens in the second line. The 27% DCR, 8.1 mo mOS, and 3.8 mo mPFS in the second line, with minimal toxicity and preserved QOL, resulted in the active investigation of SM-88 Regimen in a large, ongoing second-line trial in mPDAC (NCT04229004). Clinical trial information: NCT03512756. Research Sponsor: TYME Inc.

586   **Poster Session**

Prognosis and correlation with Ca19.9 of circulating tumor cells (CTCs) in locally advanced and metastatic pancreatic cancer.

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Background: In recent years CTCs have been extensively studied in different neoplasms. However, in PC CTCs are still emerging as a potential prognostic tool and the significance in different stages of the disease and the correlation with tumor markers are poorly understood. **Methods:** We conducted an observational, prospective, cohort study in two Spanish centers. Isolation was carried out with Isoflux technology (Fluxion Biosciences, Inc. San Francisco, CA, USA), that is combining cell separation by immunomagnetic particles (positive selection) with a microfluidic system. Before isolation, it was performed a first cell enrichment step using the density gradient cell separation technique (Ficoll). Four different markers were used, including two mesenchymal markers, EpCAM and EGFR (EMT Enrichment Kit:EpCAM/EGFR/Mesenchymal). The count of CTCs was done in a confocal microscope using the iMSRC (intelligent Matrix Screen Remote Control). A high throughput system was performed over the entire area, using a 20x objective, increasing to a 60x objective. Primary endpoint was the prognostic significance of CTCs, correlating the number of CTCs at diagnosis with overall survival. Secondary endpoints: Correlation between number of CTCs with Ca19.9/CEA values, and the difference in the median value of CTCs in metastatic compared to locally advanced disease. CTCs were analyzed at day 0 (CTC-0), just before first chemotherapy cycle was administered. **Results:** Thirty-four patients were analyzed. Clinical characteristics: Table 1. Median follow up 12.0 months. Median value of CTC-0 was 347 (range 104 - 3273) for metastatic and 436 (81 - 1082) for locally advanced patients (p = 0.942). Correlation coefficient for Ca 19.9 0.006 (p = 0.97); CEA correlation coefficient 0.191 (p = 0.303). For a cutoff of 500 CTCs, we found an AUC of 0.8 for mortality. Kaplan-Meier analysis showed an estimated median overall survival for patients with ≥500 CTCs of 8.6 months (95% confident interval [95% CI] 5.3 – 12) vs not reached for patients with < 500 CTCs (p = 0.007). HR for mortality 3.3 (95% CI 1.3 – 8.4; p = 0.011) for patients with ≥ 500 CTCs. **Conclusions:** Our data suggest 500 CTCs might be a potential cutoff for prognostic assessment. The absence of differences of CTC-0 between metastatic and locally advanced patients supports the idea of a systemic disease irrespective of the presence of metastases at diagnosis. CTC-0 seems not to correlate with tumor markers at diagnosis. Research Sponsor: Spanish Society of Medical Oncology (SEOM).

Clinical characteristics	Results
Median age (range) - years	65 (47 – 84)
Sex – no. (%)	
Male Female	18 (52.9) 16 (47.1)
Stage at diagnosis – no. (%)	
Borderline	4 (11.8)
Locally advanced	8 (34.3)
Metastatic	22 (64.7)
ECOG performance status - no. (%)	
0-1	29 (85.3)
2	5 (14.7)
CEA mg/L – median (range	4.7 (1 – 381)
Ca 19.9 U/mL – median (range)	424.50 (2 -216,100)
First-line chemotherapy	
FOLFIRINOX	14 (41.82)
Gemcitabine-nabpaclitaxel Gemcitabine	19 (55.9) 1 (2.9)

587 Poster Session

Integrative analysis of *KRAS*-wildtype pancreatic ductal adenocarcinoma reveals unique similarities to extrahepatic cholangiocarcinoma.

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Background: Oncogenic driver mutations in *KRAS* represent a hallmark genomic event in approximately 90% of pancreatic adenocarcinoma (PDAC). For the remaining 10% of patients with *KRAS* wildtype (wt) PDAC, distinct driver mutations have been described, but their transcriptional landscape has not been reported. Here, we leverage sequencing data from the PanGen trial to provide a comprehensive characterization of advanced *KRAS*wt PDAC. **Methods:** 63 patients with advanced PDAC received whole genome and transcriptome sequencing prior to treatment for metastatic disease as part of the PanGen trial (NCT02869802). Clinical features, somatic mutation data and gene expression patterns were compared between *KRAS*wt and mutant groups. PDAC samples were contrasted with 77 other metastatic carcinoma (colorectal and cholangiocarcinoma) samples from the Personalized OncoGenomics trial (NCT0215562). *KRAS* wt-associated genes were further investigated using 3 additional PDAC cohorts (COMPASS NCT02750657, TCGA, and ICGC). **Results:** 9 of 63 (14%) samples were *KRAS*wt, with an earlier median age at diagnosis (51.4 vs. 60.9 years; p=0.03). Clinical features, including diabetes, family history of malignancy, and location of primary tumor, were comparable. CA 19-9 at baseline was lower in the *KRAS*wt group, with median 58 vs. 4900 U/mL in the *KRAS*-mutant group (p=0.03). Patients with *KRAS*wt PDAC showed increased overall survival in univariable (p=0.0024) and multivariable (p=0.0089) analyses. 6 of 9 (67%) *KRAS*wt tumors had fusions involving *NRG1* (n = 3), *FGFR2* (n = 1), *BRAF* (n = 1) or *NTRK2* (n = 1), while known actionable fusions were not observed in *KRAS* mutant patients. *KRAS*wt tumors showed increased expression of genes associated with cholangiocytes and grouped with cholangiocarcinoma samples in unsupervised clustering analysis. Validation using three independent PDAC cohorts revealed a core set of 70 *KRAS* wt-associated genes that converge on keratinization, ion transport, and hormone metabolism pathways. **Conclusions:** Patients with *KRAS*wt PDAC show potentially targetable molecular traits with actionable fusions. We also highlight novel mutation and expression-based similarities between *KRAS*wt PDAC and cholangiocarcinoma samples. Recurrent dysregulation of genes involved in cellular structure and metastasis provide impetus for further investigation into the developmental trajectory and potential therapeutic vulnerabilities of *KRAS*wt PDAC. Research Sponsor: BC Cancer Foundation, Terry Fox Research Institute.

588 Poster Session

Circulating tumor DNA-based genomic landscape of early-onset pancreatic cancer.

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Background: The incidence of gastrointestinal and obesity related cancers, including pancreatic cancer, is increasing in individuals <50 years old. Early-onset pancreatic cancer (EOPC; age<50 years old at diagnosis) is characterized by higher incidence in males, enrichment for *KRAS* wild-type tumors with targetable genomic alterations (GAs), and improved outcomes compared to average-onset pancreatic cancer (AOPC; age>50 years old at diagnosis). Little is known about the genomic correlates underlying these clinical differences. In this study, we sought to characterize the circulating tumor DNA (ctDNA) landscape in EOPC compared to AOPC. **Methods:** We analyzed ctDNA samples from a total of 8548 patients (EOPC n=488 [age<30yo n=13, 30-39yo n=87, 40-49yo n=388]; AOPC n=8060) collected prospectively between December 2017 to March 2021 using a 73 gene next generation sequencing panel (Guardant360). Statistical analyses were performed using Fisher's exact test. **Results:** Of the 488 EOPC patients, 261 (53%) were male and 227 (47%) were female. Median age was 45yo in EOPC and 69yo in AOPC. Contrary to prior reports from tissue-based sequencing studies, EOPC patients were more likely to harbor *KRAS* alterations (p≤0.0001), specifically *KRAS* G12V (p≤0.0072) and *KRAS* amplifications (p≤0.0001). 1.24% of pancreatic cancer patients harbored *KRAS* G12C mutations; 0.05% were in EOPC patients. The most common currently-targetable GAs identified in EOPC were *PIK3CA* (10%), *BRCA1/2* (10%), *EGFR* (9%), *BRAF* (7%), *MET* (7%), *ATM* (7%), *FGFR1/2* (7%), *CDK6* (5%), and *ERBB2* (4%). EOPC patients had higher proportion of targetable GAs in *BRCA2* (p≤0.041), *MET* (p≤0.005), and *PIK3CA* (p≤0.0023) compared to AOPC. Conversely, AOPC patients had higher proportion of GAs in *TP53* (p≤0.0001) and *ATM* (p≤0.0001). MSI-high and TMB-high were detected in 0.07% and 0.06% of EOPC patients respectively, while 0.6% and 1.7% AOPC patients were MSI-high and TMB-high. Gene fusions were detected in 0.3% pancreatic cancer patients, predominantly in *FGFR2* (0.2%) and *FGFR3* (0.02%). Potential germline variants were detected in both EOPC and AOPC patients, most commonly in *BRCA2* (54%). Females displayed higher proportion of *TP53* (p<0.0001), *EGFR* (p<0.0029), *CDKN2A* (p<0.0001), *BRCA2* (p<0.0336) and *ATM* (p<0.0001) mutations compared to males. Gender was predictive of the pattern of GAs in EOPC with *MET* (p≤0.0027), *ARID1A* (p≤0.0376), and *BRAF* (p≤0.0034) alterations enriched in males, and *PIK3CA* (p≤0.0017) alterations enriched in females. **Conclusions:** This study represents the first large-scale blood-based ctDNA genomic profiling of EOPC. Based on this age and gender-stratified molecular characterization of pancreatic cancer, EOPC is a distinct molecular entity compared to AOPC. Identification of multiple targetable GAs may improve patient outcomes in EOPC, especially when a tissue biopsy is not feasible or sufficient for comprehensive genomic profiling. Research Sponsor: None.

589 Poster Session

Reconstructing the tumor microenvironment to unlock therapeutic options in pancreatic cancer.

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Background: Spatiotemporal heterogeneity, paucity of actionable targets, and complexity of the tumor microenvironment (TME) are major barriers to therapeutic advances in pancreatic ductal adenocarcinoma (PDAC). We reconstructed the transcriptomic data from a heterogeneous cohort of PDAC patients (pts) to examine the TME and identify putative therapeutic strategies. **Methods:** Transcriptomic profiling and targeted gene sequencing data (Tempus) on primary or metastatic specimens from PDAC pts treated at the Medical College of Wisconsin (MCW) between 2015-2020 were analyzed. Mutation calling, expression analysis, cell type deconvolution from the transcriptome, and TME reconstruction were performed using BostonGene's automated pipelines. Mann-Whitney U test and Fisher's exact test were used to assess statistical significance. **Results:** The cohort (N = 79) comprised of resectable (19%), borderline resectable (37%), locally advanced (24%) and metastatic (20%) PDAC pts. The most frequently used tumor sites for transcriptomic profiling were pancreas primary (59%), liver (16%), lung (10%) and peritoneum (10%). Four distinct subtypes were identified based on the BostonGene classification of the transcriptomic TME– Immune Enriched (IE; 14%), Fibrotic (F; 28%), Immune Enriched & Fibrotic (IEF; 36%), and Immune Depleted (ID; 22%). Analyses of the cellular composition of the TME subtypes with RNA-seq-based deconvolution showed that T-cell fractions (CD4, CD8) were higher in the IE/IEF subtypes compared to the F/ID subtypes (CD8 means: 6.4% vs 2.9%, p < 0.001; CD4 means: 15.1% vs. 7.6%, p < 0.001), while fibroblast content was higher in the F/IEF subtypes compared to the IE/ID subtypes (37.4% vs 18.4%; p < 0.001). *KRAS* wild-type (WT) tumors were enriched in the IEF subtype (58%), while *KRAS* mutated tumors comprised all four transcriptomic subtypes. Primary PDACs that underwent radiotherapy were significantly more enriched in fibroblasts compared to samples from the TCGA cohort that did not undergo radiotherapy (means: 30%(MCW) vs. 20% (TCGA), p < 0.001). Primary PDACs were enriched in the IEF subtype (46%), while liver and lung metastases were enriched in the ID (74%) and IE subtypes (70%), respectively. When pts were dichotomized to short (< 400 days) versus long (> 800 days) survivors, tumors from pts with longer survival demonstrated a trend towards enrichment in CD4/CD8 T cells and IE subtype that did not meet statistical significance. **Conclusions:** Lung metastases and *KRAS* WT PDACs harbor an immunogenic TME while liver metastases harbor an immune-cold TME, highlighting the biologic heterogeneity of PDAC. The efficacy of immunotherapeutic strategies in PDAC pts who demonstrate an IE/IEF transcriptomic subtype merits prospective evaluation. The four distinct subtypes identified by TME transcriptomic classification highlight the possibility of personalized immunotherapeutic strategies in PDAC. Research Sponsor: None.

Efficacy of MDX-124, a novel anti-annexin-A1 antibody, in preclinical models of pancreatic cancer.

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Background: Pancreatic cancer is a highly fatal disease with poor survival and response to both chemotherapy and immunotherapy. Novel approaches to treat this disease are urgently required. Annexin-A1 (ANXA1) is secreted in response to several physiological stimuli where it activates formyl peptide receptors (FPR1/2) triggering multiple oncogenic processes. High ANXA1 expression in pancreatic cancer patients is associated with poor overall survival, and influences cancer progression, drug sensitivity, migration and invasion. MDX-124 is a novel humanized antibody targeting ANXA1 and we have previously presented data demonstrating its significant antiproliferative activity. Here we present further data showing the efficacy of MDX-124 in several preclinical models of pancreatic cancer. **Methods:** *In-vitro* models utilized MIA PaCa-2, PANC-1 or BxPC-3 human pancreatic cancer cell lines. Cell cycle progression was evaluated by measuring changes in DNA content via flow cytometry. Pancreatic cancer cell viability following incubation with MDX-124 (0-10 μM) and 5FU (IC_{50}) was assessed via MTT assay. A transwell migration assay was used to evaluate the effect of MDX-124 (0-50 μM) on pancreatic cancer cell migration. *In-vivo* efficacy was evaluated using an orthotopic mouse model of metastatic pancreatic cancer (FC1242$^{luc/zsGreen}$; KPC-derived cell line) with bioluminescent imaging used to quantify the incidence and burden of lung metastases. **Results:** When compared to untreated MIA PaCa-2 pancreatic cancer cells, MDX-124 treatment decreased the proportion of cells in S-phase by 29% and G2 phase by 9.1%, with a concomitant increase in G1 of 38.1%. This occurred in a dose-dependent manner and is consistent with an MDX-124 mediated increase in cell cycle arrest. MDX-124 significantly reduced the viability of MIA PaCa-2 and PANC-1 cell lines versus an IgG control in a dose-dependent manner. Additionally in these two cell lines, combination of MDX-124 with 5FU (IC_{50}) had a significant synergistic impact reducing cancer cell viability by 99.8% and 91.2% respectively. Furthermore, MDX-124 significantly reduced the migratory ability of MIA PaCa-2 and BxPC-3 pancreatic cancer cells. In the orthotopic model of metastatic pancreatic cancer, the murine analog of MDX-124 (MDX-001), markedly reduced both the incidence and size of lung metastases. **Conclusions:** MDX-124 demonstrated significant anti-tumor efficacy in several preclinical models of pancreatic cancer as a single agent, with increased potency observed when used in combination with 5FU. Medannex will initiate a First-In-Human study in Q4 2021 to evaluate MDX-124 in solid malignancies, including pancreatic cancer. Research Sponsor: Medannex Limited.

591 **Poster Session**

Direct targeting of RAS in pancreatic ductal adenocarcinoma with RMC-6236, a first-in-class, RAS-selective, orally bioavailable, tri-complex RAS^{MULTI}(ON) inhibitor.

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Background: RAS proteins (such as KRAS, NRAS, HRAS) are small GTPases that drive cell proliferation and survival when bound to GTP. Mutant RAS proteins exist predominantly in the GTP-bound (RAS(ON)) state, leading to excessive downstream signaling via interaction with effectors such as RAF kinases. Oncogenic KRAS is required for the initiation, progression, and maintenance of pancreatic ductal adenocarcinoma (PDAC) (Hezel et al, 2006, Ying et al 2012). Although extinction of KRAS expression as well as pharmacological inhibition of RAS effectors clearly abrogate the growth of human PDAC models, clinical trials of drugs targeting key components of the RAS pathway have remained largely unsuccessful. Several factors contribute to these failures including redundancy in signaling surrogates downstream of KRAS and/or tumor complexity driven by co-occurring genomic alterations and intra-tumoral heterogeneity. **Methods:** RMC-6236 is a small molecule that binds to an intracellular chaperone protein, Cyclophilin A (CypA), resulting in an inhibitory binary complex that binds active, GTP-bound RAS to form a tri-complex and suppresses RAS signaling by disrupting interactions with effectors such as RAF kinases. **Results:** Here, we demonstrate that single agent RMC-6236, a first-in-class, orally bioavailable, RAS-selective tri-complex inhibitor of multiple RAS mutations and wild-type RAS (RASMULTI inhibitor) is highly efficacious in preclinical models of KRAS mutant PDAC (with marked activity in RAS-mutant colorectal cancer models described in Koltun et al, AACR 2021). RMC-6236 suppresses phosphorylation of ERK kinases, downstream effectors of RAS involved in cell proliferation, and induces growth suppression and apoptosis in multiple human cancer cell lines in vitro. Oral administration of RMC-6236 produces deep, durable, and dose-dependent suppression of tumor RAS pathway activation in vivo. An extended duration of tumor pharmacodynamic activity, relative to plasma exposure, is observed that likely reflects retention of RMC-6236 in tumor tissue due to high affinity binding to CypA. Daily dosing of RMC-6236 drives profound and durable tumor regressions in multiple cell line derived (CDX) and patient derived (PDX) xenograft models of KRAS mutant PDAC at doses that are well-tolerated. **Conclusions:** These results indicate that direct targeting of mutant and possibly wild-type RAS in PDAC, without inhibition of signaling nodes outside the canonical RAS pathway, has the potential to translate into clinical benefit for patients with pancreatic cancer harboring mutations in KRAS that may be superior to therapies aimed at upstream or downstream signaling elements within the RAS pathway. Our preclinical data strongly support the inclusion of PDAC patients in our planned clinical trial of RMC-6236 in patients with advanced solid tumors. Research Sponsor: Revolution Medicines.

592 Poster Session

Secretory leukocyte proteinase inhibitor: A key player in the dialogue between the tumor and its microenvironment in pancreatic cancer patients.

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Background: Secretory leukocyte proteinase inhibitor (SLPI) is a non-glycosylated pleiotropic protein with anti-protease, microbicidal, healing, anti-inflammatory and immunomodulatory activity. Previous studies have shown that SLPI is associated with pancreatic tumor progression by promoting cancer cell survival and proliferation. However, SLPI can also act on the tumor microenvironment to affect the local immune response. In the present work we evaluate the role of SLPI in patients with pancreatic cancer and its activity as a tumor escape factor from the immune response. **Methods:** Serum levels of SLPI was measured in pancreatic cancer patients by sandwich ELISA. RNA-seq was performed on 76 patient-derived xenografts (PDX) and we computed independent component analysis focusing the study on the component that best correlated with SLPI gene. Secretome analysis was performed on 38 different cell lines cells culture derived from PDX. Human monocytes were isolated and differentiated into immature dendritic cells in the presence or absence of SLPI or in the presence of a pancreatic tumor cell line that did or did not express SLPI. **Results:** The frequency distribution of serum SLPI values showed patients with low and high SLPI value (cut-off value 61.5 ng/ml). Most patients with high serum SLPI concentration had unresectable tumors. There was an indirect association between serum SLPI levels and the time of disease recurrence. The transcriptome analysis showed that expression of SLPI is associated with immune and cancer functional clusters. The analysis of the secretome showed that SLPI was present in all cell lines from PDX. The heat map of the secretome exhibited that SLPI was directly associated with factors described in tumor microenvironment and related with tumor immune evasion mechanisms, such as CSF1, SECTM1, LGALS3, IL1RN, CD59, CD55, CD46, Fas, PVR, PVRL2. Remarkably, the closest group associated with SLPI was CSF1. The latter contributes to the depressed function of antigen-presenting cells, as a result of skewed differentiation of monocytes towards macrophage-like cells rather than dendritic cells. Furthermore, *in vitro* experiments demonstrated that SLPI or SLPI-producing pancreatic tumor cell lines impaired the differentiation of human monocytes towards dendritic cells and their immunostimulatory capacity. **Conclusions:** These results suggest that SLPI may contribute to the immunosuppressive microenvironment of pancreatic cancer by acting as a tumor immune evasion factor. Clinically, this SLPI activity could be reflected in the association of the serum SLPI value with disease recurrence or progression. Research Sponsor: ANPCYT PICT-2019-03080.

593 <div align="right">**Poster Session**</div>

Extranodal extension influences prognosis in pancreatic head cancer.

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Background: Extranodal extension (ENE) is an established prognostic factor of several gastrointestinal cancers; furthermore, ENE is already included as one component of nodal category of oral cavity, penis, and vulvar cancers. However, the prognostic impact of ENE in pancreatic cancer remains unclear. In this study, we aimed to investigate prognostic implication of ENE in patients with surgically resected pancreatic cancer. **Methods:** We retrospectively reviewed electronic medical records and pathologic slides of 503 surgically resected pancreatic head cancer patients, who consecutively underwent pancreaticoduodenectomy for pathologically confirmed pancreatic ductal adenocarcinoma between January 2009 and December 2013. Patients were categorized into subgroups according to ENE status and AJCC 8th pancreatic cancer staging system. We compared the disease-free survival rates of the patients according to ENE status. Cox proportional hazard analysis was performed to evaluate prognostic factors for the disease-free survival of pancreatic head cancer. **Results:** ENE-positive patient group showed a larger tumor size, a higher rate of lymph node metastasis, and a tendency to be positive for lymphovascular invasion, perineural invasion, and resection margin ($p < 0.001$). Patients with ENE had lower overall survival (OS) and disease-free survival (DFS) rates compared with those without ENE (N0, 30 months; LN+/ENE-, 20 months; LN+/ENE+, 16 months; $p < 0.001$), (N0, 13 months; LN+/ENE-, 8 months; LN+/ENE+, 5 months; $p < 0.001$). Patients with higher N categories had lower OS and DFS rates. In addition, even in the same N stage, patients with ENE showed lower OS and DFS rates than those without ENE ($p < 0.001$). However, there was no significant difference in survival rates between patients in the N1/ENE+ group and the N2/ENE- group. Additionally, ENE was an independent prognostic factor for pancreatic cancer. **Conclusions:** ENE significantly influenced adverse prognosis among patients with pancreatic head cancer especially for those with nodal metastasis. Therefore, ENE should be considered as a prognostic factor in the future editions of the AJCC staging system. Research Sponsor: None.

Multiomic characterization to reveal a distinct molecular landscape in young-onset pancreatic cancer.

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Background: Young-onset pancreatic cancer (YOPC; $<$ 50 years at diagnosis) has been associated with male preponderance, extensive smoking history, and a trend towards improved survival compared with average-onset pancreatic cancer (AOPC; $\geq$70 years). However, the genomic and transcriptomic correlates underlying these clinical differences are incompletely understood. Using a large matched genomic-transcriptomic next-generation sequencing (NGS) dataset, we sought to characterize the distinct molecular landscape associated with YOPC compared with AOPC. **Methods:** A total of 2430 pancreatic ductal adenocarcinoma NGS samples (YOPC n = 292; AOPC n = 2138) with matched whole-transcriptome (NovaSeq) and DNA (NextSeq, 592-gene or NovaSeq, whole-exome) sequencing data were analyzed (Caris Life Sciences, Phoenix, AZ). Immune deconvolution was performed using the QuantiSeq pipeline. Limited clinical data precluded stage- and treatment-stratified comparisons between cohorts. Overall survival (OS) was obtained from insurance claims, and Kaplan-Meier estimates were calculated for age- and molecularly-defined cohorts. Significance was determined as FDR-corrected P-values (Q) $<$ 0.05. **Results:** Of 2430 PDAC patients undergoing NGS, YOPC patients (median age 46 years) were more likely to be male (65% vs. 52%; P $<$ 0.001) and current smokers (32% vs. 11%; P = 0.02) compared with AOPC patients (median age 75 years). YOPC patients had higher proportions of mismatch repair-deficient (MMR)/MSI-H (2.8% vs. 0.8%, P = 0.001), *BRCA2*-mutant (4.7% vs 2.1%, P = 0.009), and *PALB2*-mutant (1.4% vs 0.5%, P = 0.04) tumors compared with AOPC patients, while tumors in AOPC patients had more frequent *SMAD4* (20.1% vs. 14.7%, P = 0.03), *RNF43* (6.3% vs. 2.5%, P = 0.012), *CDKN2A* (24.8% vs. 19.2%, P = 0.04), and *SF3B1* (2.7% vs. 0.7%, P = 0.04) mutations. YOPC patients also demonstrated lower HLA-DPA1 homozygosity (55.2% vs. 64.1%, Q $<$ 0.05) vs. AOPC patients. Notably, YOPC patients demonstrated significantly lower incidence of *KRAS*-mutant (81.3% vs. 90.9%, Q $<$ 0.01) tumors compared with AOPC patients. In the *KRAS*-wildtype subset (n = 225), YOPC tumors were more likely to be driven by *NRG1* and *MET* fusions, while *BRAF* fusions were exclusively observed in AOPC patients. Computationally inferred immune deconvolution revealed enrichment of NK cell (Q = 0.04) and M2 macrophages (Q = 0.01) populations in YOPC tumors. There was an association with improved OS in YOPC patients with *KRAS*-wildtype (median 22.4 [YOPC-*KRAS*^{WT}] vs. 15.1 [AOPC-*KRAS*^{WT}] months, P = 0.02) but not *KRAS*-mutant (P = 0.28), tumors compared with AOPC patients. **Conclusions:** In this large real-world multi-omic characterization of age-stratified molecular differences in PDAC, YOPC is associated with a distinct molecular landscape compared with AOPC. These data reveal molecular features of YOPC with prognostic and therapeutic implications. Research Sponsor: None.

595   **Poster Session**

Prognostic utility of preoperative and postoperative circulating tumor DNA (ctDNA) in resected pancreatic ductal adenocarcinoma: A systematic review and meta-analysis.

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Background: Surgical resection offers the only chance of cure for localized pancreatic ductal adenocarcinoma (PDAC). Despite surgical resection, 80% of patients experience disease recurrence. There is growing evidence that support the prognostic role of perioperative *KRAS*-mutated circulating tumor DNA (ctDNA). We conducted a systematic review and meta-analysis to investigate the prognostic utility of preoperative and postoperative *KRAS*-mutated ctDNA testing in resected PDAC. **Methods:** Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a comprehensive search of PubMed/MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases was performed in September 2021. We included studies that reported on the effects of preoperative and postoperative *KRAS*-mutated ctDNA on overall survival (OS) and/or relapse free survival (RFS) in resected PDAC. The random-effects model was used to calculate pooled OS and RFS hazard ratios (HRs) and 95% confidence intervals (CIs). Publication bias was assessed by visual inspection of a funnel plot of the included studies. **Results:** We identified 6,986 studies, and 13 studies were eligible for analysis. A total of 954 patients were included for the final evaluation. In the preoperative setting, positive ctDNA correlated with worse RFS in 8 studies (HR, 2.067; 95% CI, 1.346-3.174; $P < 0.001$) and worse OS in 10 studies (HR, 2.170; 95% CI, 1.451-3.245; $P < 0.001$) compared to negative ctDNA. In the postoperative setting, positive ctDNA correlated with worse RFS across 7 studies (HR, 2.986; 95% CI, 1.897-4.699; $P < .001$), and worse OS in 5 studies (HR, 5.812; 95% CI, 1.757-19.228; $P = 0.004$) compared to negative ctDNA. There was visible symmetry in the funnel plot of the studies included, suggesting no publication bias. **Conclusions:** In resected PDAC, preoperative and postoperative *KRAS*-mutated ctDNA positivity may be useful markers of poor prognosis in terms of RFS and OS. Clinically, *KRAS*-mutated ctDNA testing may also have implications when considering the aggressiveness and duration of adjuvant therapy in PDAC, although prospective trials are needed to assess this utility. Research Sponsor: None.

596 **Poster Session**

Targeted therapy (TT) in patients with *KRAS* wildtype (WT) pancreatic ductal adenocarcinoma (PDAC) produces durable response.

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Background: Genomic alterations (GA) that drive cancer development and predict therapeutic response remain elusive in patients (pts) with *KRAS* WT PDAC. We interrogated our institutional database to identify actionable GAs in pts with metastatic, *KRAS* WT PDAC and analyzed the therapeutic impact of matched TT. **Methods:** We reviewed electronic medical records of *KRAS* WT PDAC pts (n=24) who underwent comprehensive genomic profiling (CGP) utilizing Foundation One CDx (25.0%) or Tempus (75.0%) between 2015-2021. Duration of response (DOR) was calculated from date of treatment (Tx) initiation to Tx discontinuation. Overall survival (OS) was measured from the date of the diagnosis (Dx) of advanced disease (AD) to death or last follow-up. OS was estimated using the Kaplan-Meier method, with at-risk periods left-truncated at the time of CGP. The effect of covariates on survival was evaluated using Cox proportional hazards regression. **Results:** Of the 24 *KRAS* WT pts, 14 (58%) had AD: 8 (57%) pts had metastatic disease at or shortly after Dx, 6 (43%) pts developed metachronous recurrence. Median age at Dx for pts with AD was 65, and 57% were female. Seven of 14 pts with AD (50%) had highly actionable GA (HAGA), (Table). Pts with HAGA demonstrated durable responses to TT (Table) with manageable toxicities. Pts with HAGA had a median OS of 28 mo compared to 5.9 mo for those without (Hazard Ratio = 0.47, p = 0.33). **Conclusions:** The sustained therapeutic benefit noted with TT matched to HAGA in pts with *KRAS* WT PDAC underscores the need for systematic interrogation of the somatic genome in PDAC pts. Optimal sequencing of cytotoxic therapy with TT and its impact on modulating clonal selection pressure in pts with *KRAS* WT PDAC merits prospective evaluation. Research Sponsor: None.

HAGA and Tx course in pts with *KRAS* WT PDAC with AD.

HAGA (n=7)	Variant Allele Frequency (%)	Chemotherapy for AD	Targeted therapy (DOR, mo)	OS (mo)
RET fusion* ATM**	-	RX3117-NAB (3.2) FOLFOX (1.8) PEGPH20-Pembrolizumab (2.9) 5-FU-NALIRI (13.5)	Praseltinib* (9.7)	33.6*
BRAF G469S	-	GEMNAB (2.3)	-	22.5
FGFR2 Fusion	-	CAPNAB (2.0) GEMCIS (8.3) 5-FU-NALIRI (1.1)	-	17.9
EGFR exon 19 deletion*	23.3	GEM (4.4)	Erlotinib* (11.4)	11.5*
BRAF V600E	10.9	5-FU-NALIRI (1.3) GEMNAB (2.8) Ipilimumab/Nivolumab (1.7)	-	8.9
BRAF N486_P490del*	28.2	GEMNAB (0.7) FOLFIRINOX (1.3)	Dabrafenib-trametinib* (4.8)	6.3*
STK11**	-	FOLFIRINOX (10.9) GEMNAB (4.5) GEMNABCIS (6.1) 5-FU-NALIRI (3.7) GEMERLOTINIB (1.6) FOLFOX*	Everolimus (1.8)	34.7*

5-FU: Fluorouracil, CIS: cisplatin, GEM: gemcitabine, NAB: nab-paclitaxel, NALIRI: liposomal irinotecan * Pt is alive, with ongoing response to treatment **germline

597 Poster Session

Detection of circulating DNA methylated *BCAT1* and *IKZF1* in pancreatic adenocarcinoma.

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Background: Pancreatic adenocarcinoma patients have poor survival outcomes and there are no non-invasive tests to aid diagnosis or therapy. Detection of circulating tumour DNA (ctDNA) methylated for *BCAT1* and/or *IKZF1* is over 60% sensitive for colorectal adenocarcinoma. Both pancreatic and colorectal adenocarcinomas are of endodermal origin, therefore, these methylated biomarkers might also have utility in detecting pancreatic cancer. The aim of this study was to investigate whether individuals with pancreatic adenocarcinoma have detectable methylated *BCAT1* and *IKZF1* DNA in circulation. **Methods:** In this pilot study, pre-treatment blood and clinicopathological findings were collected from 21 patients diagnosed with pancreatic adenocarcinoma. DNA isolated from plasma was bisulfite-converted and assayed for methylated *BCAT1*, *IKZF1* and a non-methylated region in *ACTB* (for yield estimates). Samples with methylation in either gene was deemed positive. Chi -squared test was used to compare positivity between Stage I/II and Stage III/IV cases. The sum of percent (%) methylation ([average BCAT1]+[average IKZF1])/average ACTB) ± standard error was compared between stages using Kruskal-Wallis rank test. **Results:** 10/21 (47.6%) patients were positive for methylated *BCAT1* and/or *IKZF1*. There was a trend of increasing positivity with advancing stage (Stage I/II 2/8 (25.0%) vs Stage III/IV 8/13 (61.5%, p=0.104)), and for higher % methylation with more advanced disease (Stage II 0.01%±0.004 vs Stage IV 5.0%±3.7, p=0.06). No other comorbidities or demographics were associated with positivity. **Conclusions:** Assay for methylated *BCAT1* and *IKZF1* ctDNA detects approximately two-thirds of late-stage pancreatic adenocarcinoma. Future studies are warranted to assess the clinical utility of these biomarkers for detection and monitoring of pancreatic cancer. Clinical trial information: 12616001138471. Research Sponsor: Flinders Medical Centre Foundation.

Poster Session

Comparative molecular profiling of pancreatic ductal adenocarcinoma (PDAC) of the head (H) versus body/tail (B/T) and the tumor immune microenvironment (TIME).

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Background: PDAC of the H and B/T differ in embryonic origin, cell composition, blood supply, lymphatic and venous drainage, and innervation. H tumors tend cause symptoms earlier and to present at earlier stages compared to B/T cancers. The impact of PDAC tumor location on patient presentation and survival has been shown in large national data-based analyses, although with conflicting results. We aimed to compare the molecular and tumor immune microenvironment (TIME) profiles of PDAC of the H vs. B/T. **Methods:** A total of 3499 PDAC samples were analyzed via next-generation sequencing (NGS) of RNA (whole transcriptome, NovaSeq), DNA (NextSeq, 592 genes or NovaSeq, whole exome sequencing) and immunohistochemistry (IHC, Caris Life Sciences, Phoenix, AZ). RNA deconvolution was performed using QuantiSeq (Finotello 2019, Genome Medicine) to quantify the immune cell infiltration. Pathway gene enrichment analyses were done using Gene Set Enrichment Analysis (GSEA, Subramaniam 2015, PNAS). Significance was determined as p values adjusted for multiple correction (q) of < 0.05. **Results:** Anatomic subsites of PDAC tumors were grouped by primary tumor sites into H (N = 2058) or B/T (N = 1384). There were significantly more metastatic tumors profiled from H vs. B/T (57% vs. 44%, $p < 0.001$). *KRAS* mutations (93.8% vs. 90.2%), genomic loss of heterozygosity (12.7% vs. 9.1%), and several copy number alterations (*FGF3*, *FGF4*, *FGF19*, *CCND1*, *ZNF703*, *FLT4*, *MUTYH*, *TNFRS14*) trended higher in B/T when compared to H ($p < 0.05$ but $q > 0.05$). *GNAS* mutations (2.2% vs. 0.7%) trended higher in H vs. B/T ($p < 0.05$). No significant difference in immuno-oncology (IO) markers (TMB, PD-L1, MSI-H) were observed, but expression analysis of IO-related genes showed significantly higher expression of *CTLA4* and *PDCD1* in H ($q < 0.05$, fold change 1.2 and 1.3) and *IDO1* and *PDCD1LG2* expression trended higher in B/T ($p < 0.05$, fold change 0.95). When comparing median cell abundance values as part of TIME analysis, H had increased immune infiltration of B cells (0.045 vs. 0.043), M2 macrophages (0.035 vs. 0.032), neutrophils (0.056 vs. 0.052), NK cells (0.027 vs. 0.026), CD8+ T cells (% > 0: 48.2% vs. 43.2%), while B/T had increased infiltration of M1 macrophages (0.035 vs. 0.032) (all $q < 0.05$). GSEA showed enrichment of CTLA4 (normalized enrichment score (NES) 1.6, false discovery rate (FDR) 0.19) and primary immunodeficiency pathway enrichment (NES 1.7, FDR 0.11) in H. **Conclusions:** To our knowledge, this is one of the largest cohort of PDAC tumors subjected to broad molecular profiling. Differences in IO-related gene expression and TIME cell distribution suggest that response to IO therapies may differ in PDAC arising from H vs B/T. Subtle differences in the genomic profliles of H vs. B/T tumors were also observed. Research Sponsor: None.

599 **Poster Session**

Real-world use of PARP inhibitors in BRCA1/2-mutated pancreatic cancer: A retrospective analysis.

Suvina Amin, Weiyan Li, Seongjung Joo, Gboyega Adeboyeje, Patricia DeArbeloa, Emanuel Petricoin, Edik Matthew Blais, Michael J. Pishvaian; AstraZeneca, Gaithersburg, MD; Merck & Co., Inc., Kenilworth, NJ; Perthera, Holliston, MA; Johns Hopkins University School of Medicine, Washington, DC

Background: *BRCA1* or *BRCA2* mutations can be found in approximately 6 to 8 percent of patients patients with metastatic pancreatic adenocarcinoma (mPaC). Olaparib is the only PARP inhibitor (PARPi) approved in the EU and the US as maintenance treatment for biomarker-selected patients with mPaC in the 1st line platinum-sensitive setting. However, treatment sequencing can be heterogeneous, and there is a lack of real-world data on patterns of PARPi use in relation to platinum use in BRCA1/2-mutated mPaC. **Methods:** Longitudinal records collected between 1/2012-12/2020 were analyzed for a cohort of 55 mPaC patients with *BRCA1 or BRCA2* mutations identified by commercial NGS testing who enrolled in Perthera's US real-world observational registry study. Treatment patterns including PARPi utilization and platinum-sensitivity (16 weeks without progression at any point within known history) were abstracted via physician notes across all lines of therapy. **Results:** PARPi use was documented in 60% (N=33) of 55 patients with BRCA1/2-mutated mPaC in any treatment setting. Within this cohort, 21 patients received a single agent PARPi outside of clinical trials. Among these patients, only 38% (8 of 21) transitioned to a PARPi in a platinum-sensitive context, and only 14% (3 of 21) of these transitions occurred before 2nd line. Notably, 6 patients received a PARPi in the platinum-resistant setting. Within the broader cohort, platinum-sensitive criteria was fully met for 73% (40 of 55); however, only 49% (27 of 55) reached this milestone of platinum-sensitivity prior to initiating a 2nd line therapy. **Conclusions:** The majority of these BRCA1/2-mutated patients received a PARPi-based therapy in a variety of contexts with respect to line of therapy and prior platinum history. These findings highlight the value of upfront genetic and molecular testing and the need for further exploration to identify factors associated with treatment response as well as optimized treatment sequencing. Research Sponsor: This study was funded by AstraZeneca and Merck as part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).

Plasma metabolomics to predict chemotherapy (CTX) response in advanced pancreatic cancer (PC) patients (pts) on enteral feeding for cachexia.

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Background: We evaluated the potential of plasma metabolites as predictors of response to CTX in a prospective cohort of pts who received enteral feeding for cachexia and advanced PC. **Methods:** The PANCAX-1 (NCT02400398) prospective trial enrolled 31 cachectic advanced PC pts to receive jejunal tube peptide-based diet for 12 weeks (wks) who were planned for palliative CTX. Out of 16 evaluable pts, 62.5% receiving enteral feeding met the primary endpoint of weight stability at 12 wks. As part of an exploratory analysis of the PANCAX-1 trial, serial blood samples were collected at 3 predefined timepoints over 12 wks of enteral feeding. Up to 219 plasma metabolites were analyzed by mass spectrometry and high-performance liquid chromatography. Analytes were compared by relative area under the curve (AUC) and differences evaluated by two-sample t-tests. The mean AUC was used in pts with metabolites measured from > 1 timepoint of collection. Pts were stratified by stable disease (SD), partial response (PR), or progressive disease (PD) as best overall response to standard CTX. **Results:** Of 31 pts with advanced PC prospectively enrolled for enteral feeding, there were 55 blood samples collected from 28 pts available for plasma metabolomics. 20/28 (71%) pts received first-line CTX, the majority of whom (90%) received gemcitabine-based CTX. There were 2 PRs (7%) and 10 with SD (36%) as best response to CTX. Overall, there were statistically significant differences in levels of intermediates involved in multiple metabolic pathways including glycolysis, the tricarboxylic acid (TCA) cycle, fatty acid synthesis, and nucleoside synthesis in pts with PR/SD vs. PD to CTX (all $p < 0.05$). When stratified by CTX regimen, PD to 5-fluorouracil-based CTX (e.g., FOLFIRINOX) was associated with decreased levels of essential amino acids (AAs, L-leucine, L-methionine, L-tryptophan) and non-essential AAs (L-arginine, L-serine, L-tyrosine, all $p < 0.05$). For gemcitabine-based CTX (e.g., gemcitabine/nab-paclitaxel), PD was associated with increased levels of intermediates of glycolysis (pyruvate), TCA cycle (L-glutamate), nucleoside synthesis (xanthine), and bile acid metabolism (taurocholic acid, all $p < 0.05$). **Conclusions:** We are the first to demonstrate the feasibility of plasma metabolomics in a prospective cohort of advanced PC pts on enteral feeding as their primary source of nutrition. Metabolic signatures unique to FOLFIRINOX or gemcitabine/nab-paclitaxel may be predictive of response and warrant further study. Research Sponsor: UCLA CTSI grant UL1TR001881.

601 Poster Session

Real-world timelines of BRCA1/2-related molecular testing in pancreatic cancer.

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Background: BRCA1/2 mutations are present in ~6-8% of patients with pancreatic adenocarcinoma. Olaparib is a recently approved PARP inhibitor (PARPi) in the US and Europe for germline BRCA1/2-mutated metastatic PaC in the 1st line maintenance setting following response to at least 16 weeks of a platinum-containing regimen. However, the availability of BRCA1/2 testing results at the time of 1st line and subsequent treatment decisions in the advanced stage has not been established in real-world settings. **Methods:** Longitudinal clinical/molecular data collected between 1/2012-12/2020 were retrospectively analyzed in 75 PaC pts with germline or somatic BRCA1/2 mutations (BRCA1/2m) who enrolled in Perthera's US real-world observational registry. Tumor NGS testing results were generated by commercial labs for all patients. Germline status was assessed by a molecular tumor board when testing results are available. BRCA1/2m discovery timing (days since advanced presentation), molecular testing turnaround time (days from physician order to result), and platinum utilization were abstracted from physician records. Associations between BRCA1/2m discovery timing and platinum utilization were evaluated using Fisher's exact test. **Results:** At the time of advanced PaC diagnosis, BRCA1/2m status was known in a minority of patients (29% (22 of 75). In the remaining 71% (53 of 75) patients, the median time to report BRCA1/2m status was 76 days (IQR=56-558) following advanced diagnosis. The median tumor NGS testing turnaround time was 35 days after physician order (IQR=24-54). Platinum use in any setting was documented in 85% (64 of 75) of patients and the majority of these patients (62%, 40 of 64) initiated a platinum-based regimen before BRCA1/2m status was first reported. Platinum agents were initiated before 2nd line in 75% (48 of 64) patients, and this was associated with BRCA1/2m identification before advanced diagnosis (p=0.03). **Conclusions:** BRCA1/2 testing results may not always be available when 1st line regimens are chosen which can impact ideal treatment sequencing in PaC patients. These real-world analyses underscore the importance of upfront BRCA1/2 testing in PaC patients. Research Sponsor: This study was funded by AstraZeneca and Merck as part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD).

602	Poster Session

The impact of germline and somatic mutations in the homologous recombination repair pathway in pancreatic cancer patients who undergo perioperative chemotherapy.

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Background: Limited data is available regarding the effects of germline and somatic mutations in the homologous recombination repair (HRR) pathway in patients with resectable pancreatic cancer and exactly which mutations can be targeted with platinum-based chemotherapy. We aimed to assess the impact of HRR pathway mutations in a large cohort of pancreatic patients who underwent curative intent surgical resection. **Methods:** Patients with resectable pancreatic cancer who underwent perioperative chemotherapy, diagnosed from 1999-2020 from the participating members of the Oncology Research Information Exchange Network (ORIEN) were included in the study. Patients with germline and somatic whole exome sequencing data were analyzed for known pathogenic and likely pathogenic variants according to ClinVar in the following HRR pathway genes: BRCA1, BRCA2, PALB2, BRIP1, BRAD1, ATM, RAD51C, RAD51, RAD50, CHECK2, FANCC, FANCA, MRE11 and XRCC2. The Kaplan Meier method was used to compare median overall survival (OS) between patients with adenocarcinoma, with and without HRR pathway mutations. Multivariate cox proportional hazard model was used to calculate HR and 95% CI adjusting for age at diagnosis, sex and pathologic stage. **Results:** During the study period, the ORIEN cohort included 417 patients with resectable pancreatic cancer and whole exome sequencing. Of these 313 (75%) patients had adenocarcinoma and 104 (25%) neuroendocrine tumor. A total of 19 patients (5%) had an HRR pathway mutation - 15 (5%) in the adenocarcinoma group and 4 (4%) in the neuroendocrine group. In the adenocarcinoma group, 97 (31%) patients underwent platinum-based perioperative chemotherapy. Median OS was 2.8 years (IQR 2.5-3.3) in the adenocarcinoma group without HRR pathway mutation and 3.8 years (IQR 3.4-NA) in the group with HRR pathway mutation (HR 0.6: 95% CI 0.3-1.4, p = 0.76). **Conclusions:** There was a trend towards improved survival in patients with adenocarcinoma receiving perioperative platinum-based chemotherapy with HRR pathway mutations compared to those without a mutation. This finding supports previous data in the literature regarding the prognostic role of HRR pathway alterations in pancreatic cancer. Larger prospective studies are needed to assess the predictive role of these mutations in the perioperative setting in response to platinum-based chemotherapy. Research Sponsor: None.

603 **Poster Session**

Prognostic impact of common pathologic alterations in pancreatic ductal adenocarcinoma from the veterans health administration.

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Background: The Veteran Health Administration's (VHA) National Precision Oncology Program was established to provide comprehensive molecular profiling for US military veterans with advanced cancers. There is an urgent need for precision strategies in pancreatic ductal adenocarcinoma (PDAC), as it is a leading cause of cancer-related mortality. We hypothesized that contributions of molecular alterations in PDAC would fail to stratify overall survival (OS), as current strategies are largely dependent on the activity of cytotoxic chemotherapy. **Methods:** A retrospective, multicenter cohort of 342 veterans with PDAC were identified from January 2016 to March 2021 who underwent comprehensive next-generation sequencing of tumor using FoundationOne CDx (UW IRB#2020-0696). Subjects were stratified by localized (L) or metastatic (M) disease at the time of diagnosis. Molecular alterations were compared by disease presentation using chi-squared analysis, and the clinical outcomes of overall survival (OS) were evaluated using Student's t-test. **Results:** Baseline characteristics were representative of the VA population across 80 independent sites. The cohort was male-dominant (97%) with a median age of 69 years at diagnosis. Of this sample, 55% had M disease (n=189) compared to 45% with L disease (n=153). Median OS for M PDAC was 8.9±10.2 months (mo) v. L PDAC with median OS 22.5±18.0 mo (p<0.00005). Primary driver alterations were representative of PDAC and comparable between L and M on presentation, respectively; these included *KRAS* (92% v. 91%), *TP53* (73% v. 80%), *CDKN2A* (29% v. 32%), *SMAD4* (18% v. 23%), *ARID1A* (15% v. 16%) and *BRCA2* (9% v. 12%). Primary driver alterations did not confer differences in OS across the population when comparing mutant (mt) to wildtype (wt) for *KRAS* (10.7 v. 11.8 mo, n=312), *TP53* (10.3 v. 11.8 mo, n=263), *CDKN2A* (10.2 v. 10.9 mo, n=105), *ARID1A* (10.8 v. 10.9 mo, n=53), *SMAD4* (11.3 vs 10.7 mo, n=72), and *BRCA2* (13.8 v. 10.7 mo, n=37). **Conclusions:** Using the largest report of molecular profiles in veterans with PDAC to date, current therapeutic strategies fail to differentiate clinical outcomes by common molecular alterations with cytotoxic chemotherapy. The molecular profiles of veterans are representative of PDAC and do not vary significantly between localized and metastatic disease. There remains a persistent unmet need for therapeutic strategies including ongoing investigations of novel metabolic and immune-based therapies. Research Sponsor: None.

604 **Poster Session**

Genomic classification of clinically advanced pancreatic ductal adenocarcinoma (PDAC) based on methylthioadenosine phosphorylase (*MTAP*) genomic loss (*MTAP* loss).

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Background: *MTAP* loss is represented across a wide variety of cancer types including PDAC and is an emerging target for synthetic lethality-based cancer therapies. Preclinically, *MTAP* loss leads to the accumulation of 2-methylthioadenosine, reduced protein arginine N-methyltransferase 5 (PRMT5) methylation activity and increased vulnerability to targeting of the methionine adenosyltransferase IIα (MAT2A)/ PRMT5 axis. In addition, 9p21 loss, homozygous co-deletion of *MTAP/CDKN2A* or homozygous deletion of either gene have been associated with an immunologically "cold" tumor microenvironment, primary resistance to anti PD(L)1 immunotherapy (IO) and poor prognosis phenotype (Han G, Nat Commun 2021). We investigated concurrent mutations and immune biomarkers in clinical PDAC samples with *MTAP*-loss versus -intact status. **Methods:** From a series of 177705 consecutive cases, we performed comprehensive genomic profiling on 9423 cases of PDAC using an FDA-approved assay (F1CDx) to evaluate all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on up to 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression was determined by immunohistochemistry (Dako 22C3). Furthermore, we correlated pertinent findings within a database of 16558 cases of clinically advanced cancer with *MTAP* loss. **Results:** 2003 (21.3%) of 9423 PDAC demonstrated *MTAP*-loss. Similar gender, age and number of GA per tumor were observed between *MTAP*-loss and -intact groups. Frequencies of *TP53*, *CDKN2A/B, SMAD4, PTEN* and *ARID1A* were significantly higher in *MTAP*-loss PDAC. However, previously-described biomarkers of IO efficacy (MSI, TMB, *CD274* amplification and PD-L1 expression) and resistance (*STK11, KEAP1* and *MDM2*) were infrequent and similar in both groups. The frequencies of other potentially targetable GA including *BRCA1/2, ATM, KRAS* G12C, *ERBB2, BRAF, FGFR1, NF1* and *PIK3CA* were also infrequent and similar in both groups of PDAC patients. Amongst a database of 16558 cases of clinically advanced cancer with *MTAP* loss, 1538 (9.3%) featured co-alterations in *MTAP* and *SMAD4*. 52% of the *MTAP/SMAD4* co-altered cases were PDAC. **Conclusions:** *MTAP* loss is associated with a distinctive concurrent genomic profile in PDAC and represents a potential new synthetic lethality-based opportunity for treatment with PRMT5 and MAT2A inhibitors. Furthermore, *MTAP* loss may represent an independent negative predictive biomarker for immune checkpoint inhibition in PDAC. Research Sponsor: Foundation Medicine.

	PDAC *MTAP* Intact	PDAC *MTAP* Loss	P Value
Gender	47% female/53% male	49% female/51% male	NS
Median age (range)	65.8 (22-89+)	65.5 (25-89+)	NS
CDKN2A/B	42.4%/10.5%	99.7%/95%	<.0001
TP53	76.9%	80.5%	=.0006
SMAD4	23.7%	34.2%	<.0001
ARID1A	7.8%	9.7%	=.008
PTEN	1.4%	2.5%	=.001
MSI-High/PD-L1 positive	0.5%/34.1%	0.2%/38.6%	NS
Median TMB	1.3	1.3	

605   **Poster Session**

Molecular precision medicine in pancreatic cancer: A single-center experience.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of death by cancer worldwide. Mostly diagnosed with locally advanced or metastatic disease, patients lack for treatment options. Gene alterations (GAs) are frequently observed in PDAC, some of them considered as actionable with molecular targeted therapies (MTTs), with potential clinical benefits and improved outcomes. **Methods:** We conducted a retrospective analysis of all patients, aged $\geq$18 years, with histologically confirmed PDAC, who underwent tumor molecular profiling between 2010 and 2020 in our institution as part of personalized medicine trials. Overall survival was the primary study endpoint (minimal follow-up after molecular profiling, 6 months). **Results:** Of 115 eligible patients, molecular profiling was successful in 102 patients (89%). *KRAS* mutations were the most frequent GAs, mostly G12D. Actionable GAs were found in 29 patients (28%), involving mainly *BRCA1/2* (5 [18%]), *HER2* (5 [18%]), *MTAP* (5 [18%]), and *FGFR* (3 [11%]). Only 12 of these 29 patients (41%, or 10% of the whole population) could receive MTTs accordingly, with a median progression-free survival of 1.6 months. Median OS was 17 months in patients with actionable GAs treated with MTTs (n = 12 [11.8%]), 14 months in patients with actionable GAs not treated with MTTs (n = 17 [16.7%]), and 19 months in patients without actionable GAs treated with standard therapies (n = 73 [71.5%]; p = 0.26). The absence of liver metastases was associated with better OS (HR = 0.471, p = 0.01). The longest duration of response with MTTs was observed in patients with *BRCA* mutations treated with olaparib. **Conclusions:** Actionable GAs are found in more than the quarter of patients with advanced PDAC. Overall, targeting actionable GAs with MTTs was not associated with improved OS in this retrospective study. However, selected GA/MTT duets (e.g., *BRCA* mutations/olaparib) were associated with better outcome. Research Sponsor: None.

606   **Poster Session**

The impact of CA 19-9 on survival in patients with clinical stage I pancreatic cancer.

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Background: Standard of care for early-stage resectable pancreatic cancer (PC) includes a combination of surgical resection and chemotherapy. Frequently, CA 19-9 is used as a biomarker to monitor treatment effect and has prognostic significance. We evaluated the impact of CA 19-9 on overall survival (OS) in patients with clinical stage I PC (cT1N0 and cT2N0) utilizing the National Cancer Database (NCDB). **Methods:** The NCDB was queried between 2010 and 2014 to identify patients with clinical stage I PC. Patients who had missing or undocumented CA 19-9 value at diagnosis were excluded. Demographic and clinical characteristics were analyzed. Patients were stratified into two cohorts based on the CA 19-9 value at diagnosis – CA 19-9 < 98 U/mL and CA 19-9 > 98 U/mL. Univariable and multivariable analyses were performed, and variables associated with OS were identified. Kaplan-Meier survival curves were computed to compare the OS between the two cohorts. **Results:** A total of 12,480 patients met our inclusion criteria. A majority of patients were female (51.9%), white (84.4%), with a median age of 70 years. Nearly, half the patients received care in an academic/research program (49.5%). A majority of patients had tumors located in the head of the pancreas (71.9%), and received single-agent (35.1%) or multiagent (22.9%) chemotherapy. Over half the patients (6505 patients, 52.1%) had a CA 19-9 value > 98 U/mL. A CA 19-9 value > 98 U/mL in patients predicted a significantly shorter median OS of 12.1 months compared to 19.4 months in patients with a CA 19-9 < 98 U/mL, $p<0.0001$ (Table). The 5-year OS rate was 9.9% in patients with a CA 19-9 value of > 98 U/mL compared to a 5-year OS rate of 18.1% for patients with a CA 19-9 value < 98 U/mL. On multivariable analysis, CA 19-9 > 98 compared to CA 19-9 < 98 (HR 1.53, $p<0.001$) and black race compared to white race (HR 1.10, $p<0.001$) was associated with worse survival, whereas tumor location in the body and tail compared to the head (HR 0.82, $p<0.001$), single-agent (HR 0.55, $p<0.001$) and multiagent (HR 0.55, $p<0.001$) chemotherapy compared to no chemotherapy, independently predicted improved OS. **Conclusions:** This is the first National Cancer Database study to demonstrate the prognostic value of CA 19-9 in patients with clinical stage I pancreatic cancer, with a value < 98 U/mL predicting improved survival. Clinical stage I pancreatic cancer patients appear to derive a significant benefit from chemotherapy, including single and multiagent chemotherapy, irrespective of the CA 19-9 value. Research Sponsor: None.

Survival comparison between the two Cohorts based on the CA 19-9 value.					
CA 19-9	Subjects (n= 12,480)	Median Survival (95%CI) (months)	Overall Survival (months)	Survival Rate (95% CI)	p-value
<98 U/ml	5975	19.4 (18.8, 20.3)	60 120	18.1% (16.8%, 19.4%) 0.0% (NA, NA)	<0.0001
> 98 U/ml	6505	12.1 (11.7, 12.5)	60 120	9.9% (8.9%, 10.9%) 0.0% (NA, NA)	

CA 19-9: carbohydrate antigen 19-9; CI: confidence interval.

607 Poster Session

Does detection of microsatellite instability-high (MSI-H) by plasma-based testing predict tumor response to immunotherapy (IO) in patients with pancreatic cancer (PC)?

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Background: Immunotherapy (IO) is known to have robust anti-tumor activity in patients with MSI-H solid tumors. However, clinical trials investigating IO activity have used tissue-based testing to determine MSI-H status. Pancreatic tumor biopsy often does not provide sufficient tumor tissue for MSI testing. We investigated if the MSI-H status detected by plasma-based circulating tumor DNA (ctDNA) testing predicts robust response to IO in patients with PC. **Methods:** Genomic results from a well-validated plasma-based ctDNA assay (Guardant360[G360]) performed as part of routine clinical care between October 1, 2018 and September 7, 2021 in patients with PC were queried to identify patients with MSI-H tumors. Patient characteristics, tumor characteristics, treatment details, and outcomes were reported by ordering clinicians where available. The data cut-off date was September 1, 2021. **Results:** A total of 52 patients with PC who had MSI-H tumors on G360 were identified. Clinical outcomes data were available for 10/52 (19%) patients who were included for analysis. This patient cohort had a median age of 68 years (range: 56-82); 80% were male and 80% of patients had metastatic disease. 9/10 patients received IO: 3 in the first-line, 3 in the second-line, 3 in the third-line setting; most received pembrolizumab (8/9) while 1 received ipilimumab plus nivolumab. The median duration of IO was 8 months (range: 1-24). The overall response rate was 77% (7/9) and 6 of the 7 responders continue to show response at the time of data cut-off after a median follow-up of 21 months (range:11-33). The median progression-free survival and overall survival were not reached in the IO-treated cohort. Tissue-based MSI testing results were concordant with plasma-based G360 results in 5 of 6 patients (83%) who had tissue-based test results available. The patient with the discordant result was MSI-H by G360 but had intact mismatch repair protein expression by immunohistochemistry. This patient received neoadjuvant IO followed by surgery and the resected specimen confirmed pathological complete response. **Conclusions:** The detection of MSI-H status by plasma-based ctDNA testing is highly concordant to tissue-based testing and predicts robust and durable response to IO in patients with PC. The use of a well-validated plasma-based ctDNA analysis may expand the identification of MSI-H tumors in patients with PC and enable treatment with IO resulting in improved outcomes. Research Sponsor: None.

608   **Poster Session**

Improved survival in patients with lung only recurrence after surgical resection of pancreatic ductal adenocarcinoma.

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Background: Recurrence rates after resection of pancreatic ductal adenocarcinoma (PDA) can be up to 80%. Prior data suggests that initial site of recurrence influences prognosis. This study aims to compare survival of patients (pts) with resected PDA by initial site of recurrence. **Methods:** We retrospectively reviewed the demographics, treatments, recurrence and survival of 717 pts with PDA who underwent resection at Columbia University Irving Medical Center from 2011 to 2020 and were part of a tumor registry. Analyses were performed using Kaplan-Meier and paired T-tests. **Results:** Of 717 pts with resected PDA, 320 had confirmed recurrence. Median age at diagnosis was 67 years (yrs). Among pts with a single initial recurrence site, 36 recurred in lung, 97 in liver, 95 locally, and 23 in peritoneum. 58 pts had initial recurrence at 2 or more sites. Neoadjuvant treatment had been administered in 42%, 36%, 40%, 35%, and 22% of pts with lung, liver, local, peritoneal, and multiple sites at initial recurrence, respectively (p=0.21). Adjuvant treatment had been administered in 72%, 69%, 76%, 70%, and 72% of pts with lung, liver, local, peritoneal, and multiple sites at initial recurrence, respectively (p=0.88). Pts with initial lung recurrence had a significantly longer median overall survival (mOS), 4.39 yrs, compared to initial recurrence in the liver (1.98 yrs, p=0.02), peritoneum (2.19 yrs, p=0.0002), and at multiple sites (2.66 yrs, p=0.03). A significantly longer time from diagnosis to recurrence was observed in pts who had initial lung recurrence, compared to pts who had initial hepatic, peritoneal or multiple site recurrences. Pts with initial lung recurrence had a significantly longer time from first recurrence to death compared to pts with initial peritoneal recurrence. See Table for summary. **Conclusions:** Pts with resected PDA with initial pulmonary recurrence experience improved survival compared to those who recur at other distinct or multiple sites. The underlying pathways contributing to this improved survival need to be investigated further. Research Sponsor: None.

Initial recurrence	N= 360	mOS from time of pathological diagnosis, yrs (95% CI) [p-value]	mOS from time of surgery, yrs (95% CI) [p-value]	Median time from diagnosis to first recurrence, yrs [p-value]	Median time from first recurrence to death, yrs [p-value]
Lung only	36 (11%)	4.39 (3.34-5.24)	4.18 (3.34-5.19)	2.01	1.34
Liver only	97 (30%)	1.98 (1.74-2.53) [0.02]	1.76 (1.49-2.30) [0.01]	0.90 [0.00009]	0.94 [0.3]
Local only	95 (30%)	3.15 (2.68-4.11) [0.30]	2.76 (2.34-4.04) [0.40]	1.20 [0.05]	1.45 [0.7]
Peritoneal only	23 (7%)	2.19 (1.51-2.86) [0.0002]	2.10 (0.93-2.36) [0.0001]	1.08 [0.00009]	0.82 [0.01]
Multiple Sites	58 (18%)	2.66 (2.05-3.42) [0.03]	2.34 (1.53-3.38) [0.04]	1.05 [0.0005]	0.877 [0.4]

p-values are for comparisons with lung-only recurrence

609 Poster Session

Homologous recombination repair pathway alterations and their relationship to homologous recombination deficiency in advanced pancreatic cancer patients.

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Background: Homologous recombination repair (HRR) is critical for limiting DNA damage arising from double strand breaks. Disrupting HRR has emerged as a therapeutic strategy in pancreatic cancer given the development of PARP inhibitors that can specifically target tumors with homologous recombination deficiency (HRD). While HRD is strongly associated with loss-of-function mutations in BRCA1/2, a broad range of pathogenic alterations have been identified in other HRR genes. Identification of pathogenic alterations that predict response to PARP inhibition remains a critical knowledge gap in the field. **Methods:** We retrospectively analyzed de-identified records from 895 patients with advanced pancreatic cancer that underwent next generation sequencing (NGS) with the TempuslxT assay (DNA-seq of 648 genes at 500x coverage, matched normal, full transcriptome RNA-seq). HRD-positivity and genome-wide loss of heterozygosity (LOH) were compared across groups, which were defined based on alterations to BRCA1/2 or other HRR pathway genes. **Results:** We identified 293/895 (33%) pancreatic cancer patients to be HRD-positive. Among HRD positive patients, 23/895 (2.6%) tumors harbored two alterations in BRCA1/2 (BRCA++), 179/895 (20%) harbored a single alteration in BRCA1/2 (BRCA+), 25/895 (2.8%) harbored two alterations in at least one other non-BRCA HRR gene (other HRR++), 367/895 (41%) harbored a single alteration in one other HRR gene (other HRR+), and 143/895 (16%) had pathogenic alterations in neither BRCA1/2 nor other HRR genes. In terms of HRD status, 23/23 (100%) of BRCA++ cases, 179/337 (53%) of BRCA+ cases, 4/25 (16%) of other HRR++ cases, and 87/367 (24%) of other HRR+ cases were HRD-positive. We observed no cases that were HRD-positive without an alteration in either BRCA1/2 or other HRR gene. Within the other HRR+ group, we found that single alterations in CHEK1/2, FANCA/L, MRE11, PALB2, and RAD51B were all significantly associated with HRD-positivity whereas CDK12, for instance, was not (Table). **Conclusions:** Comprehensive genomic profiling demonstrates that approximately 1 in 4 patients without BRCA alterations may potentially benefit from PARP inhibition due to alterations in other HRR genes. Future studies may examine the role of PARP inhibition in this population of HRR+ pancreatic cancer patients. Research Sponsor: None.

HRR+ Gene	Overall (n = 367)	HRD Negative (n = 280)	HRD Positive (n = 87)
CDK12	15 (4.1%)	9 (3.2%)	6 (6.9%)
CHEK1	42 (11%)	21 (7.5%)	21 (24%)
CHEK2	108 (29%)	64 (23%)	44 (51%)
FANCA	35 (9.5%)	21 (7.5%)	14 (16%)
FANCL	31 (8.4%)	12 (4.3%)	19 (22%)
MRE11	47 (13%)	25 (8.9%)	22 (25%)
PALB2	46 (13%)	22 (7.9%)	24 (28%)
RAD51B	64 (17%)	39 (14%)	25 (29%)

610 Poster Session

Spatially defined enrichment of a neuronal-like malignant phenotype in pancreatic cancer after neoadjuvant treatment.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is highly lethal and resistance to chemotherapy and radiotherapy is a major obstacle to improving clinical outcomes. Hence, there is an urgent need to elucidate the gene expression programs, spatial context, and interactions among different cell types in residual disease after neoadjuvant treatment. **Methods:** We optimized and applied single-nucleus RNA-seq (snRNA-seq) to 43 frozen primary PDAC tumors. Eighteen were treatment-naïve, 14 received FOLFIRINOX followed by radiotherapy with 5-FU or capecitabine (CRT), and 5 were subjected to CRT combined with losartan on protocol (CRTL). We performed unsupervised clustering of single nucleus profiles and then annotated and quantified cell subsets. Malignant and fibroblast gene expression programs were identified by consensus non-negative matrix factorization (cNMF). We mapped our cell type signatures and expression programs onto the tumor architecture using whole-transcriptome digital spatial profiling (DSP) to uncover distinct multicellular spatial neighborhoods and intercellular interactions that compose PDAC and are remodeled by neoadjuvant treatment. **Results:** Consistent with treatment effect, the proportion of malignant cells was significantly lower in tumors treated with neoadjuvant therapy. Within the immune compartment, CRTL was associated with a higher fraction of CD8$^+$ T cells and Tregs compared to untreated and CRT tumors. Differential expression analysis of CD8$^+$ T cells revealed greater effector function (e.g., *IL2, CCL4, CCL5*) and reduced quiescence/dysfunction markers (e.g., *TIGIT, TCF7, KLF2, LEF1*) associated with CRTL. We discovered expression programs across malignant and fibroblast profiles that formed a refined molecular taxonomy, including a novel neuronal-like malignant program enriched in the neoadjuvant groups and associated with the worst prognosis in independent cohorts. *Ex vivo* treatment of organoids derived from an untreated PDAC with FOLFIRINOX chemotherapy and radiotherapy recapitulated enrichment of the neuronal-like program. Whole-transcriptome DSP revealed three distinct multicellular neighborhoods: classical, squamoid-basaloid, and treatment-enriched. The observed enrichment in post-treatment residual disease of multiple spatially-defined receptor-ligand interactions and a neighborhood featuring colocalization of the neuronal-like malignant program, neurotropic CAF program, and CD8$^+$ T cells may open new opportunities for therapeutic targeting in PDAC. **Conclusions:** Our work provides a high-resolution molecular framework for understanding the inter- and intra-tumoral heterogeneity of pancreatic cancer, spatial organization into discrete multicellular communities, and treatment-associated reprogramming as a blueprint for exploring novel therapeutic strategies tailored to residual disease. Research Sponsor: Lustgarten Foundation., Other Foundation.

611 **Poster Session**

High-plex proteomic prognostic marker discovery for patients with pancreatic cancer adenocarcinoma using digital spatial profiling.

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Background: The long-term outcomes following surgical resection for Pancreatic Ductal Adenocarcinoma (PDAC) remain poor, with only 20% of patients surviving 5 years after pancreatectomy. With its immune-privileged nature, starting from the early pre-neoplastic state, it appears to escape easily from the antitumor immune response. Despite rationale for targeting immune pathways in PDAC, there has been little benefit observed at this point. The aim of the current study was to interrogate immune landscape of PDAC utilising the Nanostring GeoMx Digital Spatial Profiler (DSP), a state-of-the art analysis platform enabling Hi-plex proteomic characterisation whilst maintaining tumor microenvironment (TME) topographical features. **Methods:** We assessed Formalin Fixed Paraffin Embedded (FFPE) tumor samples from 28 treatment-naive PDAC cases represented in a multi-regional tissue microarray (TMA) for which extensive IHC, molecular, genomic characterisation and clinicopathological follow-up data is available. Following multiplex IHC staining for DAPI, panCK, aSMA and CD3 to guide region selection, we employed the GeoMx DSP system (NanoString) to select regions within multiple TMA cores. We quantified 60 immune markers simultaneously in multiple tissue compartments defined by immuno-fluorescence co-localization including (tumor [panCK+ve], immune stroma (PanCK-ve]. Data analysis was performed by a combination of DSP analysis suite and custom R pipeline. **Results:** The spatially informed variable assessment by DSP was validated by both regression and variable prognostication compared with IHC for stromal CD3, CD8 CD68 in near serial TMA PDAC sections. Unsupervised analysis of DSP proteome data in the panCK-negative regions identified an immune poor group associated with shorter Overall Survival (OS) (13.0 versus 31.1months, P = 0.005). When transcriptomic subtype was considered, the checkpoint inhibitor B7-H3 was significantly upregulated in the squamous subtype tumours versus the classical group (Log2: 1.63, P = 0.001). Patients with high B7-H3 expression, using a median expression cut-off, were associated with shorter OS on multivariate analysis (Hazard Ratio: 4.16, P = 0.01) including lymph node and resection margin status, a finding that was validated in an external cohort at the transcriptome level. **Conclusions:** This pilot scale discovery study shows the potential of the Nanostring DSP technology in the identification of spatially-informed biomarkers with prognostic relevance in biopsy sized samples from treatment-naive PDAC. We identified a number of relevant candidate immune predictors in spatial context that are currently undergoing validation in larger independent cohorts and the neoadjuvant setting. Future studies will apply this technology to pre- and post-treatment biopsy samples. Research Sponsor: Cancer Research UK.

Association of pancreatic adenocarcinoma location (head/body/tail) with DDR mutation status and response to platinum-based therapy.

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Background: Pancreatic adenocarcinoma is an aggressive disease with poor clinical prognosis that can originate from either the head (H) or body/tail (BT). Potential prognostic implications for H versus BT tumors have been reported; however, the molecular underpinnings associated with these differences in survival have not fully been explored. Using a large-scale real-world cohort of H and BT tumors with NGS results available from commercial labs, we retrospectively aim to identify potential differences between H and BT tumors in their response to standard therapies to help understand whether the treatment prioritization for pancreatic adenocarcinoma should take into account anatomical sidedness, as is recognized today with left-sided versus right-sided colorectal cancers. **Methods:** We analyzed outcomes across 1540 pts with NGS results from Perthera's Real-World Evidence database who were diagnosed with PDAC originating from the H or BT. Progression-free survival (PFS) was evaluated from initiation of 1st line for advanced disease until discontinuation due to disease progression. Hazard ratios and p-values were computed via Cox regression when comparing PFS between 1st line FOLFIRINOX and gemcitabine/nab-paclitaxel. Differences in frequencies of genomic alterations between proximal and distal were analyzed by Fisher's exact test. **Results:** Mutations in *BRCA1/BRCA2/PALB2* were enriched (unadjusted p-value=0.017) in BT tumors (8.6% of 619) relative to H tumors (5.4% of 921). An expanded set of DDR pathway alterations (e.g. *ATM, FANCA, CHEK2, BAP1, BRIP1*, etc) were also enriched (unadjusted p-value=0.003) in BT tumors (21.4% of 619) relative to H tumors (15.6% of 921). In BT tumors, mPFS on 1st line FOLFIRINOX was longer (Table) than 1st line gemcitabine/nab-paclitaxel (p=0.0078) but this difference was not observed in H tumors (p=0.34). Overall survival data in these patients and an independent institutional cohort which motivated these analyses will also be discussed. **Conclusions:** DDR pathway alterations are known predictors of increased benefit from platinums and these real-world insights preliminarily suggest that DDR mutations are more common in BT vs. H. Prospective studies may be warranted to confirm the hypothesis-generating findings that platinum-based regimens should be prioritized in patients with BT tumors while underscoring the importance of routine NGS testing in both BT and H tumors given the prevalence of DDR pathway alterations on both sides of the pancreas. Research Sponsor: None.

TreatmentGroup	Tail(n)	Tail mPFS [95% CI] (months)	Head(n)	Head mPFS [95% CI] (months)
1st Line FOLFIRINOX	182	9.9 [7.5-12.1]	192	8.9 [6.8-10.3]
1st LineGem/nab-Pac	178	7.2 [6-8.3]	196	7.5 [6.9-8.7]
FOLFIRINOX vs Gem/nab-Pac		p=0.0078(HR=0.67 [0.5-0.9])		p=0.34(HR=0.87 [0.66-1.16]

613 Poster Session

Association of pretreatment CA19-9 with survival after 3-fraction SBRT for locally advanced pancreatic cancer: Results from a phase I dose-escalation trial.

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Background: The optimal dose and fractionation scheme for stereotactic body radiotherapy (SBRT) is unknown. The biologic effects of ultra-high doses per fraction (>8Gy) are theoretical, but may include eliciting an effect on the endothelial cells of the tumor vasculature which could improve treatment response. This study aimed to determine the safety and maximally tolerated dose of 3-fraction SBRT for locally advanced pancreatic cancer (LAPC). **Methods:** A multi-site phase 1 dose escalation trial was conducted from March 2016 to April 2019 at Memorial Sloan Kettering Cancer Center (NCT02643498) and University of Colorado (NCT02873598). Patients with localized histologically confirmed pancreatic adenocarcinoma deemed unresectable on multidisciplinary review without distant progression following induction chemotherapy for $\geq$ 2 months were eligible. Patients received 3-fraction LINAC-based SBRT at 3 dose levels, 27Gy, 30Gy and 33Gy following a modified 3+3 design, allowing for enrollment of additional patients at the last dose level during the 90-day observation period, provided no dose-limiting toxicities (DLTs) were observed. DLTs were defined as $\geq$ Grade 3 treatment-related GI toxicity within 90 days of RT by CTCAE v.4. The secondary endpoints were overall survival (OS), local progression-free and distant metastasis-free survival (LPFS and DMFS, respectively). Univariate analysis using log-rank test was performed to identify factors associated with OS. **Results:** Twenty-three evaluable patients were enrolled, including 8 patients at 27Gy, 8 patients at 30Gy and 7 patients at 33Gy. The median age was 67 years (range 52 - 79), 9 patients (39%) were male, all were stage IIIwith a median tumor size of 3.5cm (range, 1.0 - 6.4) and CA19-9 of 60U/mL (range, <1 - 4880). All received chemotherapy for a median of 4.0 months (range 2.5 -11.4). There were no grade $\geq$ 3 abdominal pain, dyspepsia, diarrhea, nausea, vomiting, or gastrointestinal hemorrhage. Four patients underwent resections (pancreaticoduodenectomy=3, Appleby=1). Twelve-month rates of OS, DMFS and LPFS were 45.8 %, 37.7% and 53.0%, respectively. On univariate analysis, CA19-9 (HR=0.2365, 95%CI 0.07999 to 0.6990), but not dose level, size, N stage, tumor location, duration of chemotherapy were associated with OS. Twelve-month OS for patients with CA19-9 $\leq$ 60U/mL vs > 60U/mL were 80% vs 27% (p=0.0023). **Conclusions:** For select LAPC patients, dose escalation to the target dose of 33Gy in 3 fractions resulted in no DLTs and disease outcomes comparable to conventional RT. Lower pre-SBRT CA19-9 values were associated with improved OS and could help identify patients most likely to benefit from local therapies. Continued exploration of (ultra)hypofractionated schemes to maximize tumor control while enabling efficient integration of RT with systemic therapy is warranted. Clinical trial information: NCT02643498/NCT02873598. Research Sponsor: Institutional support – internal grants.

614   **Poster Session**

KRAS mutation methylation clonality in early-stage pancreatic cancer.

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Background: *KRAS* is mutated in 90% of pancreatic cancers making it a seemingly ideal target for treatment and yet, with the exception of the rare G12C mutation, *KRAS* is undruggable for the vast majority of pancreatic patients. Herein, we characterize, *in silico*, KRAS methylation-derived mutation clonal and subclonal diversity in PDAC and examine their impact upon clinical outcomes. **Methods:** We developed a mutation methylation (MM) clonality workflow for gene mutation assignment as clonal versus subclonal and applied it genome-wide to TCGA data. For comparison, we used the cancer cell fraction (CCF) clonality prediction. We examined clinical outcomes by comparing in months (mos), Kaplan-Meier estimated overall survival (OS) using a log-rank test and a cox model for testing several features. We performed differential gene expression, differential gene correlation, and gene set enrichment analyses (GSEA) between KRAS MM clonal versus subclonal early stage pancreatic patients. **Results:** Using 104 TCGA early stage pancreatic cancer patient tumors from TCGA with mutation, methylation and clinical outcomes data, we defined KRAS MM clonality (n = 70 clonal, n = 34 subclonal) and CCF clonality (n = 74 clonal, n = 28 subclonal) tumors. Clonality assignment between methods was 53% clonal and 17% subclonal concordant, and 19% discordant among samples. KRAS MM clonality was associated with significantly (p = 0.046) shorter OS (median OS = 11.5 mos) as compared to the KRAS subclonal group (median OS = 15 mos). By comparison, KRAS CCF clonal and subclonal patient groups did not differ in their OS. When RNA-Seq derived subtypes for pancreatic cancer were included in a model with our KRAS MM clonality marker, only our marker remained as significantly associated with OS. Median KRAS gene expression was significantly (p = 0.01) higher in the KRAS MM clonal versus subclonal group. A GSEA showed enrichment of *MYC* targets in the KRAS clonal group. We identified 72, mostly protein coding genes residing on chromosomes 5q, 7p and 8p that correlated with KRAS gene expression only in the subclonal group. **Conclusions:** Our analyses shows a potential clonality dissection of the established 90% KRAS mutation rate in pancreatic cancer, which based on our MM workflow, may be dissected into 61% KRAS clonal and 30% KRAS subclonal. By assigning clonality based on another DNA data type using CCF, we obtain 65% KRAS clonal and 25% KRAS subclonal. Thus, regardless of which DNA-based workflow, overall, the KRAS clonality rates are similar. There is a notable difference however in patient-level assignment of KRAS clonality as only our workflow showed poor OS associated with KRAS clonality. The introduction of a methylation-based mutation clonality marker could prove invaluable when used in combination with methylation-based circulating tumor DNA assays for patient and treatment selection, and clinical trial monitoring of tumor responses. Research Sponsor: Cancer Prevention and Research Institute of Texas #RR160093 (to S. Gail Eckhardt), Department of Oncology, Dell Medical School, Research Funds (to J. Kowalski-Muegge)

615   **Poster Session**

Pancreatic cancer: Cutaneous metastases, clinical descriptors and outcomes.

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Background: The occurrence of cutaneous metastasis from pancreatic cancer (PC) is rare, and the exact incidence is unknown. The literature to date is primarily limited to isolated case reports. Herein, we evaluate the clinical, genomic, and other descriptors of patients with PC and cutaneous metastases. **Methods:** Institutional databases were queried using search terms "pancreas cancer" and "cutaneous mets". Clinical history, demographics, PC cutaneous metastasis details, and survival outcomes were abstracted. Results were described using descriptive statistics, and overall survival (OS) from the diagnosis of cutaneous metastasis was estimated using Kaplan-Meier methods. **Results:** Of 140 on initial search, 40 patients met inclusion criteria of PC and cutaneous metastases and were analyzed. The median age (Q1-Q3, IQR) of pancreatic cancer diagnosis was 66.0 (59.3-72.3, 12.9) years. Most common histologic subtype was adenocarcinoma (n= 39, 98%), and one patient had a neuroendocrine malignancy. Most patients had stage IV disease at diagnosis (n=26, 65%). The most common location of the primary tumor was tail of the pancreas (n=17, 43%). Forty-eight percent (n= 19) had cutaneous metastasis at/within one month of cancer diagnosis. Most patients received chemotherapy (n=37, 93%), with 14 patients (35%) patients also receiving local therapy in the form of local excision or radiation. The most common cutaneous metastasis site was the abdomen (n=40, 66%), with umbilical lesions occurring in 58% (n=23) of abdominal lesions. The median interval (Q1-Q3, IQR) between diagnosis of pancreatic cancer and development of cutaneous metastasis was 1.4 (0-14.5, 14.5) months. The median OS (95% CI) from cutaneous metastasis diagnosis was 11 months (7.0, 20). Table details the observed differences between umbilical vs. non-umbilical metastases. Sixteen of 40 (40%) patients underwent somatic testing. The most frequently mutated genes were *KRAS* (n= 16, 100%), *TP53* (n=7, 44%), *CDKN2Ap14ARF* (n=5, 31%), *CDKN2Ap16INK4A* (n=5, 31%), and *CDKN2B* (n=3, 19%). Germline testing was undertaken in 12 (30%) patients, and pathogenic variants were observed in 3: *CHEK2* (n=1, 8%), *BRCA1* (n=1, 8%), and *ATM* (n= 1, 8%). Summary of cutaneous metastasis characteristics. **Conclusions:** Cutaneous metastases from PC are rare and can be present at the time of diagnosis of stage IV disease, occurring most frequently in the umbilicus. Cutaneous metastases can be classified into umbilical and non-umbilical metastases, which may be due to a different biology. Research Sponsor: Cancer Center Support Grant/Core Grant P30 CA008748.

	Umbilical metastases n=23 (58%)	Non-umbilical metastases n=17 (43%)
Stage at diagnosis		
I, II, III	6 (26%)	8 (47%)
IV	17 (74%)	9 (53%)
Location of primary tumor		
Head, neck	6 (26%)	6 (35%)
Body, tail	17 (74%)	10 (59%)
Unknown	0 (0%)	1 (6%)
Median OS (95% CI) in months	14 (7.0, 29)	8.9 (4.1, –)

Retrospective study of survival outcomes in patients with hereditary pathogenic and variants of unknown significance mutations in pancreatic adenocarcinoma.

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Background: Since 2019, all patients with pancreatic adenocarcinoma (PDAC) are recommended to undergo germline testing per the National Comprehensive Cancer Network guidelines. Outside of PARP inhibitors in germline BRCA mutated PDAC, the predictive and prognostic implications of these genetic alterations are unclear. Many hereditable mutations are continually discovered, but the majority are considered Variants of Unknown Significance (VUS). The purpose of this retrospective study is to characterize the clinical characteristics of multiple pathogenic and VUS germline mutations in PDAC. **Methods:** An IRB approved institutional database of PDAC patients (n=442) was queried for patients diagnosed between 2007 and 2021. Only patients who tested positive for hereditary mutations (n=35) or VUS (n=41) were included. Patients with both pathogenic mutation and VUS were considered in the pathogenic mutation group. **Results:** 76 patients (35 pathogenic, 41 VUS) were included in the analysis. Pathogenic mutations were divided into subcategories including DNA repair (n=21), polyposis (n=2), pancreatitis-associated (n=11), and other (n=2). With a mean follow-up period of 636 days, the overall survival (OS) for pathogenic mutations at 90 days, 180 days, 1 year, and 2 years was 100%, 97.1%, 88.6%, and 74.3% respectively. The cumulative recurrence was 2.9%, 11.4%, 22.9%, and 37.1%. For VUS, the OS was 97.6%, 95.1%, 75.6%, and 56.1% and cumulative recurrence was 0%, 14.6%, 31.7%, and 43.9% in the same time intervals. **Conclusions:** This data suggests that patients with germline mutations may have favorable outcomes when compared to the general population. Overall germline alterations in our intuitional cohort had a 2-year survival of nearly 75%. Notably, pancreatitis-associated hereditable mutations consisted a sizeable portion of our overall cohort. Although current therapy is most focused on DNA repair mechanisms, these results show that other novel germline genetic alterations may be prognostic and warrant further investigation. Research Sponsor: None.

Gene	DNA repair				Polyposis			Pancreatitis			Other		
	ATM	BRCA1/2	CHEK2	MUTYH	RAD51C	APC	MSH2	CFTR	CTRC	SPINK1	CDKN2A	CDHB	VUS
N	7	9	3	1	1	1	1	9	1	1	1	1	41
Stage	IA/IB				IIA/IIB			III			IV		
Pathogenic	11.4% (4/35)				20% (7/35)			22.9% (8/35)			45.7% (16/35)		
VUS	26.8% (11/41)				14.6% (6/41)			14.6% (6/41)			43.9% (18/41)		
	90 Day				180 Day			1 Year			2 Year		
Overall Survival (Pathogenic)	100% (35/35)				97.1% (34/35)			88.6% (31/35)			74.3% (26/35)		
Recurrence (Pathogenic)	2.9% (1/35)				11.4% (4/35)			22.9% (8/35)			37.1% (13/35)		
Overall Survival (VUS)	97.6% (40/41)				95.1% (39/41)			75.6% (31/41)			56.1% (24/41)		
Recurrence (VUS)	0% (0/41)				14.6% (6/41)			31.7% (13/41)			43.9% (18/41)		

617   **Poster Session**

Clinical characteristics, treatment, and oncological outcomes in patients with ampullary cancer at a reference center in Mexico.

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Background: Ampullary cancer (AC) represents 0.2% of gastrointestinal cancers. Given the rarity of the disease, information regarding treatment strategies and outcomes derives from studies that include the different types of periampullary cancers, which constitute a heterogeneous group. Our aim was to describe the clinical characteristics, treatment modalities and outcomes in patients (pts) with true AC treated at our institution. **Methods:** A retrospective review of medical records of all consecutive pts with histological diagnosis of AC evaluated at our institution from Jan 2009-Dec 2019. Clinical, pathological and laboratory variables at diagnosis were recorded. Overall survival (OS) was estimated by Kaplan-Meier and compared with the Log-rank test. Statistical significance was determined at $P<0.05$. **Results:** 133 pts with AC were included. Median age was 62 yo (IQR 53-70), 51.9% were women. 25% had ampullary adenoma history. Symptoms at diagnosis: 89% jaundice, 63% weight loss and 56% abdominal pain. Median laboratory values were total bilirubin 1.7 mg/dL (0.7-5.1), albumin 3.7 g/dL (3.1-4.2), hemoglobin 12.6 g/dL (10.9-14.2), carbohydrate antigen (CA) 19-9 34.7 U/mL (6.4-113.9) and carcinoembryonic antigen (CEA) 2.6 ng/mL (1.2-4.2). Most tumors were moderately differentiated (59%). Histologic subtypes of adenocarcinoma were available in 84 pts: intestinal 46.4%, pancreaticobiliary 39.3% and mixed 14.3%. Stage at diagnosis was localized (46%), locally advanced N+ (29%) and advanced (25%). For those with localized/locally advanced disease, 91% (91/100) underwent surgical resection, 25.3% (23/91) received adjuvant chemotherapy (ChT), 69.6% (16/23) received single agent and 30.4% (7/23) duplet. Pts who received adjuvant Cht presented N+ in 69.6%, moderate differentiation in 73.9%, intestinal 47.8% and pancreaticobiliary subtype 43.5%. In advanced setting, 63.6% (21/33) received palliative Cht, 66.7% received a duplet regimen. Median OS was 32.8 (22.9-42.8) months (mos). Median OS according to stage was 152.1, 28.1 and 10.2 mos for localized, locally advanced, and advanced, respectively ($P<0.001$). OS univariate analysis is shown in table. **Conclusions:** Most of pts presented with localized/locally advanced disease, were eligible to surgical resection and had a better survival. For those with N+ disease it is required to evaluate the role of adjuvant Cht. In the advanced setting, Cht improves prognosis. Research Sponsor: None.

	Odds Ratio	Interval	P value
Age ≥ 60 *vs* <60 yo	1.89	0.93 – 3.82	0.07
Abdominal Pain Yes *vs* No	0.39	0.19 – 0.81	0.01
Nausea Yes *vs* No	0.41	0.18 – 0.91	0.02
Total bilirubin ≥ 2.0 *vs* <2.0 mg/dL	1.70	0.84 – 3.44	0.13
CA 19-9 ≥ 30 *vs* <30 U/mL	3.06	1.31 – 7.14	0.008
CEA ≥ 2.0 *vs* <2.0 ng/mL	3.11	0.73 – 13.1	0.11
Histologic grade Moderate/poor *vs* well	1.28	0.27- 2.23	0.64
Lymph nodes Yes *vs* no	2.59	1.13 – 5.92	0.02
Stage Advanced vs Localized/Locally advanced	20.54	4.6 – 90.5	<0.001

618   **Poster Session**

Unraveling the oligometastatic phenotype and its association with pancreatic cancer survival.

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Background: Stage IV pancreatic ductal adenocarcinoma (PDAC) carries a dismal prognosis with a reported five-year survival of 2%. While treated as a monolithic population, a subset of stage IV patients exhibit a superior response to chemotherapy. In fact, anecdotal studies have shown that a well-selected subset of patients with oligometastatic disease of the liver and/or lung may benefit from more aggressive locoregional therapies. However, the definitions of oligometastatic disease utilized are arbitrary and exhibit a high degree of inter-study variation. In this study, we aim to advance a data-based definition of oligometastatic disease to support novel therapeutic approaches. **Methods:** Our institutional cancer registry was queried to identify consecutive patients diagnosed with pathologically confirmed stage IV PDAC (2015-2019). Pre-treatment cross-sectional imaging was reviewed and up to 10 liver and/or lung metastases were quantified while > 10 metastases was considered innumerable. Metastases to the peritoneum, bone, non-regional lymph nodes and other distant metastatic sites were recorded. A multivariable Cox regression model was used to assess the association of the number of isolated liver and/or lung metastases with overall survival (OS). Using time-dependent receiver operative characteristic (t-ROC) curves, we evaluated all of the subjects with isolated liver/lung metastasis for each cut-off (1-10) to identify the threshold most capable of predicting OS. Kaplan-Meier curves were used to visualize the patient survival function and the log-rank test was applied to test the statistical significance. **Results:** 183 patients with complete pre-treatment cross-sectional imaging available for review were included in this retrospective study. Amongst them, only 167 patients had complete treatment records and were included in the final multivariable analysis. 43% (72/167) of patients were treated with FOLFIRINOX, 38% (63/167) with gemcitabine/nab-paclitaxel, and 19% (32/167) elected best supportive care. Patients with ≤5 isolated liver/lung metastases had improved OS compared to patients with > 5 liver/lung metastases and/or other sites of distant metastasis (HR 0.48, 95% CI: 0.32, 0.76; p = 0.001). t-ROC analysis showed that a cut-off of ≤5 isolated liver/lung metastases was most predictive of survival at 12 (AUC 0.77) and 18 months (AUC 0.78) after diagnosis. Median OS of patients with ≤5 liver and/or lung metastases (n = 32) and > 5 liver/lung metastases and/or additional sites of metastasis (n = 135) was 13.7 vs. 5.8 months, respectively (p = 0.0004). **Conclusions:** In this study, we propose an anatomically-based definition of oligometastatic disease for stage IV PDAC patients. Our data showed that patients with ≤5 isolated liver/lung metastases have a more favorable prognosis and may benefit from early consideration of multimodal therapy intensification. Research Sponsor: U.S. National Institutes of Health.

TPS619   **Trials in Progress Poster Session**

A phase II, open-label pilot study evaluating the safety and activity of liposomal irinotecan (Nal-IRI) in combination with 5-FU and oxaliplatin (NALIRIFOX) in preoperative treatment of pancreatic adenocarcinoma: NEO-Nal-IRI study.

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Background: Neoadjuvant treatment for potentially curable pancreatic cancer (PDAC) is increasing in acceptability, but a standard regimen has yet to be established. Multiple studies have demonstrated feasibility and effectiveness of the FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen in the perioperative setting. However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given pre-op. Liposomal irinotecan injection (Nal-IRI) in combination with 5FU/LV is FDA approved with a well-tolerated safety profile in relapsed, refractory metastatic PDAC. The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen (NALIRIFOX) and to demonstrate safe and effective neoadjuvant delivery. **Methods:** This phase 2, open-label, multicenter single-arm study focuses on patients (pts) with operable PDAC without metastatic disease. Other key eligibility criteria include age ≥18 years, resectability confirmed by multiD GI tumor board (resectable vs. borderline), adequate cardiac, renal, hepatic function and ECOG performance status of 0 to 1. Pts receive NALIRIFOX regimen as per the table every 2 weeks for four months followed by disease reassessment. Pts who remain surgical candidates will undergo surgical resection within 4 to 8 weeks following last dose of therapy. The primary endpoint is to assess safety and feasibility of regimen in pre-op setting. Secondary endpoints include R0 resection rate, clinical, biochemical and radiological response rate and patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale. Exploratory ctDNA and stool microbiome analyses are also planned. Enrollment continues to a maximum of 28 evaluable pts to demonstrate a reduction in historical 30-day post-op complication rate. Clinical trial information: NCT03483038. Research Sponsor: Ipsen Biopharmaceuticals, Inc., University of Florida Health Cancer Center.

NALIRIFOX regimen components given intravenously (IV) every 14 days.		
Agent	**Dose**	**Route/Duration**
Nal-IRI	50 mg/m^2	IV over 90 minutes
Oxaliplatin	60 mg/m^2	IV over 120 minutes
Leucovorin	400 mg/m^2	IV over 120 minutes
5-fluorouracil infusion	2400 mg/m^2	IV continuous infusion for 46 hours

TPS620   **Trials in Progress Poster Session**

A phase 1/2 study to evaluate the safety, tolerability, and preliminary efficacy of GP-2250 in combination with gemcitabine for advanced or metastatic pancreatic adenocarcinoma.

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Background: GP-2250 is a metabolic enzyme inhibitor that selectively induces oxidative stress, mitochondrial dysfunction, and apoptosis in cancer cells by inhibiting glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and limiting aerobic glycolysis, an essential process for energy production in cancer cells. In vitro, increasing concentrations of GP-2250 induced proportional dose-response effects in 5 different pancreatic cancer cell lines (Buchholtz *BMC Cancer* 2017). Patient-derived pancreatic xenograft studies in mice demonstrated tumor growth inhibition with GP-2250 monotherapy (Braumann *J Clin Oncol* 2020). In combination with gemcitabine, a synergistic effect was shown with greater inhibition of pancreatic tumor growth than with either gemcitabine or GP-2250 alone. These findings support the assessment of the therapeutic potential of GP-2250 in combination with gemcitabine in patients with pancreatic cancer. **Methods:** This open-label phase 1/2 trial will evaluate the safety and tolerability of escalating doses of GP-2250 and the preliminary efficacy of GP-2250 in combination with gemcitabine in patients with advanced unresectable or metastatic pancreatic adenocarcinoma who have progressed on prior treatment with *FOLFIRINOX* chemotherapy. In phase 1, Bayesian Optimal Interval design will be used for GP-2250 dose escalation. The dose-limiting toxicity (DLT)–assessment period will be 5 weeks at each dose level (starting dose 250 mg once weekly intravenously), consisting of a 1-week run-in period with GP-2250 monotherapy, followed by a full cycle of GP-2250 plus standard dose and schedule of gemcitabine. Single patient cohorts (100% dose escalation between cohorts) will be enrolled until the occurrence of the first DLT (or cohort 4 if no DLTs occur in cohorts 1−3), after which, cohorts will be expanded to 3 patients with 35%−45% dose escalations between cohorts. Patients will receive treatment until disease progression or development of unacceptable toxicity. Primary study endpoints include safety and tolerability of GP-2250, tumor response (RECIST 1.1), disease control rate (complete response, partial response, stable disease), and duration of response. Pharmacokinetics, incidence and severity of laboratory abnormalities and treatment-emergent adverse events, progression-free survival, and overall survival will also be assessed. As of September 2021, 19 patients have been enrolled. Following completion of the phase 1/2 trial, a phase 3 first-line maintenance study will be initiated. This study is funded by Geistlich Pharma AG. Clinical trial information: NCT03854110. Clinical trial information: NCT03854110. Research Sponsor: Geistlich Pharma AG.

TPS621   **Trials in Progress Poster Session**

Randomized phase II study of nalicap (nal-IRI/capecitabine) compared to NAPOLI (nal-IRI/5-FU/LV) in gemcitabine-pretreated advanced pancreatic cancer: Trial-in-progress.

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Background: Liposomal irinotecan (nal-IRI) in combination with fluorouracil (5-FU) and folinic acid (LV), called the NAPOLI regimen, improves survival in advanced pancreatic cancer patients who failed gemcitabine-based chemotherapy (Wang-Gillam A et al. 2016). Capecitabine is an oral anti-cancer agent as the prodrug of 5-FU. Capecitabine has proven its efficacy in gastrointestinal cancers like stomach cancer, colon cancer, or pancreatic cancer. Replacing continuous 5-FU infusions with oral capecitabine with equivalent efficacy has been tested and is now widely used. However, in pancreatic cancer, replacing continuous infusion of 5-FU with an oral drug has not yet been tested. Therefore, this trial is being conducted with the aim of improving patient convenience while maintaining efficacy, when the continuous infusion of 5-FU/LV in NAPOLI (nal-IRI/5-FU/LV) regimen are replaced with oral capecitabine. This study is a two-arm, open-label, multicenter, randomized phase 2 trial to assess whether capecitabine plus nal-IRI combination treatment (NaliCap) is non-inferior to NAPOLI regimen in gemcitabine-pretreated patients with advanced pancreatic cancer. **Methods:** Eligible patients have histologically confirmed pancreatic adenocarcinoma who have failed to gemcitabine-based chemotherapy. This trial is composed of two parts: safety lead-in-part and randomization part. NaliCap regimen consists of administration of capecitabine twice daily for day 1-14 and intravenous administration of nal-IRI for day 1 every 3weeks. To figure out recommended phase 2 dose of the NaliCap combination regimen, the safety lead-in-part is being conducted as a 3+3 design. In the randomization part, patients will be assigned to NAPOLI or NaliCap in a 1:1 ratio. The planned enrollment is 184 patients in the randomization part. Patients allocated to the NaliCap group will receive recommended phase 2 dose of NaliCap determined through the safety lead-in-part. Patients allocated with the NAPOLI group will receive nal-IRI $70mg/m^2$ intravenously day 1, LV $400mg/m^2$ IV day 1, and continuous 5-FU $2400mg/m^2$ infusion over 48hours every 2weeks. Response assessments are performed every 6 weeks using the RECIST criteria version 1.1 (every 2 cycles in the NaliCap group and every 3 cycles in the NAPOLI group). The primary endpoint is progression-free survival, with a non-inferior margin of the hazard ratio of 1.4. Key secondary endpoints are overall response rate, disease control rate, overall survival, safety, and quality of life. This study is prospectively registered at ClinicalTrials.gov, NCT04371224. Clinical trial information: NCT04371224. Research Sponsor: None.

TPS622   **Trials in Progress Poster Session**

Phase 1b expansion study of CX-5461 in patients with solid tumors and *BRCA2* and/or *PALB2* mutation.

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Background: BRCA and PALB2 proteins play important roles in the maintenance of genomic stability as they are essential for error-free repair of double-stranded DNA breaks, while deficiency of these proteins promotes error-prone DNA repair, chromosomal instability and carcinogenesis. Inherited mutations in BRCA genes predispose to various early onset cancers. Poly(ADP-ribose) polymerase inhibitors (PARPi) inducing synthetic lethality in tumors with homologous recombination (HR)-mediated DNA repair deficiencies have been approved for treatment in patients with germline BRCA-mutated metastatic pancreatic adenocarcinoma. Unfortunately, resistance to PARPi associated with multiple mechanisms can be observed over time, suggesting a prominent unmet need for the development of new treatment options. CX-5461, a G-quadruplex stabilizer, employs an alternative mechanism in destabilizing the DNA replication fork to promote DNA damage resulting in cancer cell lethality in HR-deficient (HRD) tumors, thus represent a promising therapeutic strategy for patients with defects in HR-repair. **Methods:** A prior phase I dose escalation study has been completed for CX-5461 (CCTG IND.231, NCT02719977) but additional safety data are required to define the chronic tolerable dose for phase 2 trials. Therefore, a phase Ib expansion trial was designed for two doses preselected from our previous phase I trial to determine the final recommended phase II dose (RP2D) by evaluating safety, tolerability and objective response rate in a more selected population. This trial will enroll patients in two cohorts; the main cohort recruiting patients with pancreatic, breast, ovarian or prostate cancer with germline BRCA2 and/or PALB2 mutation, and an exploratory cohort recruiting ovarian cancer patients with BRCA1 and/or other HRD-associated mutations. Major eligibility criteria include documented evidence of pathogenic or likely pathogenic germline mutation in BRCA2 and/or PALB2 for main cohort patients, documented evidence of pathogenic or likely pathogenic germline mutation or a clinically actionable somatic mutation in BRCA1 and/or other HRD-associated mutation for exploratory cohort. Patients with non-adenocarcinoma histology of pancreatic cancer, known photosensitivity disorders of the skin, or patients with ophthalmological conditions will not be enrolled. An initial 16 eligible patients for the main cohort and 10 eligible patients for the exploratory cohort will be enrolled in parallel to receive CX-5461 at 250mg/m2, delivered via IV infusion on Day 1 and Day 8 of a 28-day cycle. Upon completion of the initial arms with no safety concerns, another two arms will open to enroll an additional 16 patients for the main cohort and 10 patients for the exploratory cohort to receive CX-5461 at 325mg/m2 of the same dosing schedule. Clinical trial information: NCT04890613. Research Sponsor: Senhwa Biosciences, Inc., Other Foundation.

TPS623   **Trials in Progress Poster Session**

A phase 2, multicenter, open-label study evaluating trastuzumab deruxtecan (T-DXd) for the treatment of select human epidermal growth factor receptor 2 (HER2)-expressing solid tumors (DESTINY-PanTumor02).

Funda Meric-Bernstam, Chiedozie Anoka, Anna Dobrowolska, Anubhavini Chaudhry, Jacqui Rowbottom, Mark Gustavson, Soham D. Puvvada; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; AstraZeneca Pharmaceuticals, Gaithersburg, MD; AstraZeneca Pharma Poland Sp. z oo, Warsaw, Poland; AstraZeneca Pharmaceuticals, Cambridge, United Kingdom

Background: Human epidermal growth factor receptor 2 (HER2) is an established therapeutic target in both breast and gastric cancer. However, HER2-targeting therapies are not approved beyond these malignancies despite a high prevalence of HER2 expression across cancers of epithelial origin. Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload. In a cohort of pretreated patients with multiple HER2-expressing tumors, T-DXd demonstrated promising antitumor activity, with an investigator-assessed confirmed objective response rate of 40.9% (9 of 22 patients) and median progression-free survival of 11.1 months (95% CI, 5.4-20.5 months; Tsurutani J, et al. *Cancer Discov.* 2020;10:688-701). Here we describe the phase 2 DESTINY-PanTumor02 trial evaluating T-DXd in patients with select HER2-expressing solid tumors. **Methods:** DESTINY-PanTumor02 (NCT04482309) is an open-label, multicenter, multicohort, phase 2 study evaluating T-DXd for the treatment of patients with select HER2-expressing locally advanced, unresectable, or metastatic tumors. The study will consist of 7 cohorts of patients (n≈40 each) with urothelial bladder, biliary tract, cervical, endometrial, ovarian, pancreatic, or rare tumors (tumors excluding those in the other cohorts and breast, gastric, colorectal, and non-small cell lung cancer). Patients are required to have disease progression following ≥1 prior systemic treatment for advanced or metastatic disease or have no satisfactory alternative treatment options. Prior HER2-targeting therapy is allowed. The primary endpoint is investigator-assessed confirmed objective response rate per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints include duration of response, disease control rate, progression-free survival (all per investigator assessment according to RECIST 1.1), overall survival, safety, pharmacokinetics, and immunogenicity. Previously presented at the ESMO Congress 2021, FPN: 1869 TiP, Meric-Bernstam et al. Reused with permission. Clinical trial information: NCT04482309. Research Sponsor: AstraZeneca.

TPS624   **Trials in Progress Poster Session**

A multi-institutional, single-arm, phase II trial of neoadjuvant modified-FOLFIRINOX for resectable pancreatic ductal adenocarcinoma.

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Background: Within the next decade, pancreatic ductal adenocarcinoma (PDAC) is expected to rise to the second leading cause of cancer-related mortality. To increase the survival, various peri-operative treatments have been tested, and adjuvant FOLFIRINOX or gemcitabine plus capecitabine is now standard of care after surgical resection for localized PDAC. Even with superior survival among various disease extent of PDAC, resectable PDAC still shows poor outcomes with surgery followed by adjuvant chemotherapy. This phase II study is investigating the role of modified-FOLFIRINOX as neoadjuvant treatment for resectable PDAC. **Methods:** This study is a phase II, multi-institutional, single-arm trial to evaluate the efficacy and safety of modified-FOLFIRINOX in resectable PDAC. The main inclusion criteria are histologically confirmed PDAC; resectable PDAC confirmed by both computed tomography (CT) and magnetic resonance imaging (MRI) according to NCCN guideline resectability criteria (no arterial tumor contact to celiac axis, SMA or CHA; no tumor contact with SMV or PV or $\leq 180°$ contact without vein contour irregularity); no previous treatment (surgery or chemotherapy); ECOG 0 or 1; and adequate organ function. Patients receive oxaliplatin 85 mg/m^2 D1 + leucovorin 400mg/m^2 D1 + irinotecan 150 mg/m^2 D1 + 5-FU 2,000 mg/m^2 46h continuous infusion, every other week for 6 cycles (12 weeks). Response assessments are performed every 6 weeks using the RECIST criteria version 1.1. Baseline MRI, PET-CT scan before treatment, and pre-surgery MRI after 6 cycles are mandatory. The primary endpoint was R0 resection rate. Secondary endpoints included progression-free survival, overall survival, disease-free survival, objective response rate, safety, resection rate, and correlative biomarker exploration. The study will enroll up to 27 patients and is currently recruiting at four sites in South Korea. As of September 2021, 20 patients have been enrolled. Clinical trial information: KCT0004421 (Registration ongoing for clinicaltrials.gov). Research Sponsor: None.

TPS625   **Trials in Progress Poster Session**

A monocentric, first-in-human (FIH), safety and preliminary efficacy study of (neo)adjuvant, model-based, whole-body hyperthermia (WBHT) treatment in advanced solid cancer patients or stage IV metastatic pancreatic adenocarcinoma patients.

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Background: Whole-Body Hyperthermia (WBHT) represents the only hyperthermia modality available for patients with disseminated malignancies. The rationale for the treatment of malignant disease by heat is based on a direct cell-killing effect at temperatures in the range of 41– 42°C and driven by a number of reasons. Phase-I mining and phase-I veterinary (dog) clinical study proved the safety of WBHT treatment alone and in combination with standard of care therapy in dogs with cancer. A systematic review addressed clinical trials that used WBHT in pancreatic cancer patients. In these trials, the weighted estimate of the treated population median overall survival was 11.7 compared to 5.6 for the control cohorts. **Methods:** The is a first in-human, mono-centric, non-randomized trial to establish the safety and preliminary efficacy of WBHT treatment with the TempoCure (medical device) alone in patients with advanced solid cancer (cohort A) or in combination to SOC chemotherapy treatment in patients with stage IV metastatic pancreatic adenocarcinoma (cohort B). The study of 12 to 20 patients is not powered for any statistical analysis. The analysis will be limited to descriptive statistics, considered the doses provided and the extra blood sampling taken at different time points. The treatment is applied under deep anaesthesia in a unit connected to the operating room at the hospital. Cohort A1. Three patients with advanced solid cancer will be subjected to repetitive WBHT starting with 2 hours (day 1), 4 hours (day 8) and 6 hours (day 15) using the TempoCure to keep the patient at a temperature of 41.5°C. The patient's body temperature will be monitored by specific sensors (liver, oesophageal, rectal and cutaneous). Cohort A2. The highest WBHT duration with acceptable side effects from cohort A1 will be applied to three additional patients with advanced solid cancer, once a week and for 15 days in total. Cohort B1. Three pancreatic cancer patients will be subjected to repetitive WBHT starting with 2 hours (day 1), 4 hours (day 8) and 6 hours (day 15) using the TempoCure to keep the patient at a temperature of 41.5°C and in combination with the standard of care chemotherapy. Cohort B2. The highest WBHT duration with acceptable side effects from cohort B1 will be applied in combination with chemotherapy to three pancreatic cancer patients, once a week and for 15 days in total. Major inclusion criteria are: Adequate liver structure (confirmed by CT scan) allowing the placement of the liver sensor; Adequate coagulation defined as; PT (%) ≥ 70%; aPTT ≤ ULN; Von Willebrand Factor Antigen ≥ LLN; Von Willebrand Factor Activity ≥ LLN; PFA COL/EPI CT ≤ 1.15 ULN; PFA COL/ADP CT ≤ 1.15 ULN. Enrollment to Cohort A1 began in July 2021. Clinical trial information: NCT04467593. Research Sponsor: ElmediX.

TPS626   **Trials in Progress Poster Session**

Phase Ib/II trial of siltuximab and spartalizumab in patients in metastatic pancreatic cancer.

Mehmet Akce, Walid Labib Shaib, Maria Diab, Olatunji B. Alese, Christina Wu, Sunisha Thomas, Emily Greene, Cameron Herting, Gregory B. Lesinski, Bassel F. El-Rayes; Winship Cancer Institute, Atlanta, GA; Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; Emory University, Atlanta, GA; Winship Cancer Institute of Emory University, Atlanta, GA; Emory University, Winship Cancer Institute, Atlanta, GA; Winship Cancer Institute, Emory University, Atlanta, GA

Background: Interleukin-6 (IL-6) is associated with carcinogenesis, immune suppression, and poor prognosis in pancreatic adenocarcinoma (PDAC). Preclinical data demonstrated dual inhibition of IL-6 and (programmed death ligand-1) PD-L1 facilitates CD8+ T cell migration into pancreatic tumors and was effective in controlling tumor growth in syngeneic and genetically engineered PDAC mouse models. Siltuximab is a chimeric monoclonal antibody which targets the IL-6 molecule specifically and spartalizumab is a high-affinity ligand-blocking humanized IgG4 antibody against the PD-1 receptor. Based on this preclinical rationale, we developed a phase Ib/II trial to determine the recommended phase II dose (RP2D), evaluate the safety, toxicity profile, preliminary antitumor activity, and immunogenicity of the siltuximab and spartalizumab in patients with previously treated metastatic PDAC. **Methods:** The phase Ib trial design is standard 3+3. Primary endpoint is to determine RP2D. Siltuximab is administered intravenously (IV) in three dose levels of 6 mg/kg (DL1), 11 mg/kg (DL2), 9 mg/kg (only if 2 DLTs observed on DL2) every 3 weeks with spartalizumab at 300 mg IV every 3 weeks. Eligible patients must have stage IV PDAC who have failed at least one prior therapy age ≥18 years, ECOG PS 0-1, no prior anti PD-1 or anti-PD-L1 agent. After RP2D is established, an expansion phase will enroll 24 patients with PDAC. Pre and on-treatment biopsy will be performed in 24 patients in the expansion cohort for correlative analysis. Pre-treatment and on-treatment peripheral blood samples will be collected from all patients. In the expansion phase patients will receive initial cycle (every 3 weeks) treatment with either spartalizumab or spartalizumab plus siltuximab and then starting cycle 2 all patients receive the combination following the on-treatment research biopsy. This design will enable us to evaluate the immunological effects of spartalizumab alone versus the combination in the tumor microenvironment and peripheral blood. This study was activated in January 2020 and to date 12 patients were enrolled in dose escalation phase. The dose expansion phase has recently started accrual. Clinical trial information: NCT04191421. Research Sponsor: EUSA Pharma, Novartis.

TPS627   **Trials in Progress Poster Session**

Randomized multicenter phase II/III study of gemcitabine plus nab-paclitaxel or modified FOLFIRINOX or S-IROX in patients with metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE).

Akihiro Ohba, Masato Ozaka, Junki Mizusawa, Hiroshi Katayama, Takuji Okusaka, Satoshi Kobayashi, Masafumi Ikeda, Shuichi Kaneko, Naoki Sasahira, Naohiro Okano, Masayuki Furukawa, Ikuya Miki, Nobumasa Mizuno, Ichiro Yasuda, Nao Fujimori, Tomoko Kataoka, Makoto Ueno, Hiroshi Ishii, Haruhiko Fukuda, Junji Furuse; Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan; Department of Gastroenterology, Cancer Institute Hospital, Tokyo, Japan; JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan; Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan; Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Gastroenterology, Graduate School of Medicine, Kanazawa University, Kanazawa, Japan; Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan; Department of Hepatobiliary-Pancreatology, National Hospital Organization, Kyushu Cancer Center, Fukuoka, Japan; Department of Gastroenterology, Hyogo Cancer Center, Hyogo, Japan; Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan; Third Department of Internal Medicine, University of Toyama Hospital, Toyama, Japan; Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Clinical Research Center, Chiba Cancer Center, Chiba, Japan

Background: Pancreatic cancer is one of the most dismal cancers with few effective drugs. Both FOLFIRINOX (FFX) and gemcitabine plus nab-paclitaxel (GnP) showed superiority in overall survival (OS) to gemcitabine in phase III studies and became the standard of care for first-line chemotherapy. However, to date, there is no prospective randomized controlled studies comparing FFX and GnP. In addition, the original FFX has the problems of high toxicity and complicated administration, and we have been developing modified FFX with dose reduction of irinotecan and without bolus fluorouracil and S-IROX, which replaces continuous intravenous fluorouracil with orally administered fluoropyrimidine of S-1. The modified FFX showed median OS of 11.2months [95% confidence interval (CI), 9.0-not calculated] as good as the original FFX in a phase II study, and the S-IROX showed a high objective response rate (ORR) of 57.1% (95% CI, 34.0–78.2%) in a phase I study. This phase II/III study aims to confirm the superiority of modified FFX and S-IROX to GnP in metastatic or recurrent pancreatic cancer. **Methods:** The main eligibility criteria are metastatic or recurrent pancreatic cancer, histologically diagnosed as adenocarcinoma or adenosquamous carcinoma, no prior chemotherapy for pancreatic cancer, Eastern Cooperative Oncology Group Performance Status 0 or 1, and age 20-75 years old. Enrolled patients are randomized 1:1:1 to GnP, modified FFX, or S-IROX. GnP is consisted of nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) on days 1, 8, and 15, every 4 weeks, modified FFX is consisted of oxaliplatin (85 mg/m^2), irinotecan (150 mg/m^2), l-leucovorin (200 mg/m^2), and fluorouracil (2400 mg/m^2, 46-hour continuous infusion), every 2 weeks, and S-IROX is consisted of oxaliplatin (85 mg/m^2), irinotecan (150 mg/m^2) and S-1 (80 mg/m^2, days 1-7), every 2 weeks. All regimens are administered until disease progression or unacceptable toxicity. The primary endpoint of the phase II part is the ORR to S-IROX with the null hypothesis of a threshold ORR of less than 20%, which decide whether to proceed to the phase III part in three arms or two arms (GnP and modified FFX). The primary endpoint of the phase III part is OS, and secondary endpoints are progression-free survival, ORR, incidence of adverse events (AEs) and serious AEs, and dose intensity. We calculated a sample of 732 patients to maintain 80% power at a one-sided alpha error of 2.5% in each comparison, and the hazard ratios of modified FFX and S-IROX versus GnP were estimated at 0.73 each. The study started patient accrual in April 2019 and 349 patients have been enrolled as of September 2021. Clinical trial registry: jRCTs031190009. Clinical trial information: jRCTs031190009. Research Sponsor: Japan Agency for Medical Research and Development.

TPS628   **Trials in Progress Poster Session**

An open, single-center, exploratory clinical trial to evaluate the safety and efficacy of RNA CAR-mesothelin T cells in patients with advanced refractory pancreatic cancer.

Hui Yang, Liting Guo, Chenfei Zhou, Xiaojun Liu, Yangbing Zhao, Jun Zhang, Yan Shi; Department of Oncology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; UTC Therapeutics Inc, Shanghai, China

Background: Pancreatic cancer is an aggressive gastrointestinal cancer characterized by late diagnosis initially, prone to distant metastasis and poor prognosis. The current treatment of pancreatic cancer is very limited, resulting in its 5-year survival rate of less than 10%. It is necessary to seek new treatment methods and treatments. Chimeric antigen receptor T (CART) cell therapy has made a breakthrough in hematological malignancies. Therefore, the goal of this clinical trial is to study the safety, efficacy and pharmacokinetics of mRNA-engineered anti-Mesothelin Chimeric Antigen Receptor T-Cell (anti-MESO CAR-T cells) therapy in patients with mesothelin expression-positive, advanced pancreatic tumors that have failed at least first-line or second-line therapy. **Methods:** The study will adopt the "3+3" dose escalation design exploring two doses of 1×10^9 and 3×10^9. The administration is planned to infuse 3 times a week for 2 consecutive weeks. The subjects will receive a total dose of 1×10^9 RNA transduced anti-MESO CAR-T cells in the first week, following lymphodepleting chemotherapy with cyclophosphamide 300 mg/m^2/day and fludarabine 30 mg/m^2/day given over 3 days by intravenous infusion. If there is no obvious dose-limiting toxicity (DLT) after the first week of infusion, three times consecutive infusions of 1×10^9 anti-MESO CAR-T cells each time is planned in the second week. Each subject needs to be observed for at least 2 weeks (14 days) after completing the last infusion. Lymphodepleting chemotherapy will not be repeated prior to additional infusions of anti-MESO CAR-T cells. Clinical trial information: 04981691. Research Sponsor: UTC Therapeutics Inc.

PANOVA-3: A phase 3 study of tumor treating fields (TTFields) with gemcitabine and nab-paclitaxel (GnP) for front-line treatment of locally advanced pancreatic adenocarcinoma.

Vincent J. Picozzi, Teresa Macarulla, Philip A. Philip, Carlos Roberto Becerra, Tomislav Dragovich; Virginia Mason Hospital and Medical Center, Seattle, WA; Hospital Universitario Vall d'Hebron, Barcelona, Spain; Barbara Ann Karmanos Cancer Institute, Detroit, MI; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Banner MD Anderson Cancer Center, Gilbert, AZ

Background: Tumor Treating Fields (TTFields) are a non-invasive, loco-regional antimitotic therapy approved for the treatment of glioblastoma and malignant pleural mesothelioma. TTFields (150–200 kHz) are delivered via arrays placed on the skin surrounding the tumor site. *In vitro*, TTFields (150 kHz), with or without chemotherapy, had antiproliferative and anticlonogenic effects on pancreatic cancer cells. The Phase 2 PANOVA study (NCT01971281) demonstrated the safety and preliminary efficacy of TTFields combined with nab-paclitaxel and gemcitabine (GnP) in both metastatic and locally advanced pancreatic adenocarcinoma (LAPC). **Methods:** The Phase 3 PANOVA-3 trial (NCT03377491) will evaluate the efficacy and safety of adding TTFields to GnP in a larger group of patients with LAPC. This prospective, randomized trial is currently enrolling 556 patients with unresectable LAPC (per National Comprehensive Cancer Network guidelines), Eastern Cooperative Oncology Group performance status of 0-2, and no prior progression or treatment. Patients will be randomized 1:1 to receive TTFields plus GnP or to GnP alone, stratified by performance status and geographical region. A recent protocol amendment included the use of a smaller, more light-weight (reduced from 6 to 2.7 lbs.) TTFields device. Standard doses of nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) will be administered on days 1, 8, and 15 of a 28-day cycle. TTFields (150 kHz) will be delivered $\geq$ 18 h/day until local disease progression per Response Evaluation Criteria In Solid Tumors Criteria V1.1. Follow-up visits will be conducted every 4 weeks; a computed tomography scan of the chest and abdomen will be performed every 8 weeks. After local disease progression, patients will be followed for survival on a monthly basis. The primary endpoint is overall survival (OS). Secondary endpoints include progression free survival (PFS), local PFS, objective response rate, 1 year survival rate, pain- and puncture-free survival rate, rate of resectability, quality of life, and toxicity. The sample size calculation used a log-rank test comparing time to event in patients treated with TTFields plus GnP with control patients on gemcitabine alone. PANOVA-3 is designed to detect a hazard ratio of 0.75 in OS. Type I error is set to 0.05 (2-sided) and power to 80%. Study locations in Austria, Belgium, Canada, Croatia, Czech Republic, France, Germany, Hong Kong, Hungary, Israel, Italy, Poland, Spain, Switzerland, and the US are currently recruiting. Clinical trial information: NCT03377491. Research Sponsor: Novocure Inc.

TPS630   **Trials in Progress Poster Session**

NeoOPTIMIZE: An open-label, phase II trial and biomarker discovery platform to assess the efficacy of adaptive switching of modified FOLFIRINOX (mFFX) or gemcitabine/nab-paclitaxel (GA) as a neoadjuvant strategy for patients with resectable/borderline resectable and locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC).

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Background: Neoadjuvant chemotherapy (NAC) and/or chemo-RT may confer benefit to patients with localized PDAC, by better tolerability, tumor down-staging, and increased R0 resections. mFFX or GA are the current NAC backbones; however, a lack of robust predictive biomarker(s) hampers identification of patients most likely to benefit from mFFX or GA. Further, desmoplastic stroma/poor vascularity compromise NAC efficacy, but angiotensin II receptor inhibitor, losartan, might remodel vascular perfusion to enhance chemotherapy activity. We designed the NeoOPTIMIZE trial for patients with newly diagnosed localized PDAC to provide a flexible clinical platform to: 1) evaluate the feasibility and efficacy of early switching of mFFX to GA, and 2) establish a robust biomarker/imaging discovery platform to optimize the NAC backbone. **Methods:** NeoOPTIMIZE is an open-label, non-randomized, phase II trial to assess the efficacy of an adaptive treatment strategy that allows for early switching of NAC in patients with localized PDAC. Sixty patients (n = 40 resectable/BRCP; n = 20 locally advanced unresectable [uLAPC]) will be enrolled to receive 2 months of preoperative mFFX (oxaliplatin, 85 mg/m^2; folinic acid, 400 mg/m^2; irinotecan, 150 mg/m^2; 5-FU, 2400 mg/m^2), then restaging by a multidisciplinary tumor board (multiD-TB). Absent progression (by panc protocol CT and CA19-9 decline/increase $< 30\%$ from baseline), patients continue mFFX (4 cycles). If progression (by panc protocol CT; CA19-9 increase $> 30\%$), patients switch to GA (nab-paclitaxel, 125 mg/m^2; gemcitabine, 1000 mg/m^2) for 2 months. After 4 months of mFFX or mFFX/GA, another restaging multiD-TB will decide to proceed with: a) RT (if vascular involvement) then resection, b) resection, or c) continued chemo (if unresectable). Losartan (50 mg PO QD) is given throughout NAC and RT regimens. The primary endpoint estimates the proportion of resectable/BRPC patients with R0 resection. Assuming that the proportion of R0 is 60%, a sample size of 32 will provide a 95% CI of 0.41 - 076. To account for a 20% dropout, 40 patients will be enrolled towards primary endpoint. A separate exploratory cohort of 20 uLAPC patients will be enrolled. Secondary endpoints include DFS, PFS, OS, and AEs. Exploratory objectives include correlating clinical outcomes data with changes in blood-based biomarkers (CA19-9, ctDNA, circulating tumor cells etc.) and research DCE-MRI. We are collecting tumors to correlate deep multiomic analytics with clinical data. The study is open with 6 patients enrolled at time of submission. Clinical trial information: NCT04539808. Research Sponsor: American Association for Cancer Research (15-90-25-BROD), Pancreatic Cancer Action Network, Brenden-Colson Center for Pancreatic Care, Knight Precision Oncology.

TPS631   Trials in Progress Poster Session

A phase I study to evaluate the safety and tolerability of SX-682 in combination with PD-1 inhibitor as maintenance therapy for unresectable pancreatic adenocarcinoma.

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Background: Survival outcomes for advanced pancreatic ductal adenocarcinoma (PDAC) remain dismal despite improvements in systemic therapy regimens developed over the past decade. In addition, current first-line therapies result in cumulative cytopenias and neuropathy, highlighting the need for more effective, less toxic maintenance treatment strategies. There are currently no standard approved maintenance treatments for patients with PDAC not associated with BRCA or DNA-repair mutations. Preclinical data suggest a potential synergistic effect of combining blockade of CXC chemokine receptors (CXCR) with immunotherapy or chemotherapy in pancreatic cancer[1,2]. We are currently conducting a Phase I study (NCT04477343) evaluating SX-682, an oral CXCR1/2 inhibitor, and Nivolumab as maintenance treatment for advanced PDAC. **Methods:** This is an open-label, dose escalation Phase I clinical trial evaluating the combination of SX-682 and Nivolumab. Patients must have histologically confirmed unresectable PDAC and have completed at least 16 weeks of first-line chemotherapy with disease stability or treatment response at time of enrollment. Radiographically measurable disease must be present per iRECIST criteria. Patients receive a 3-week run-in phase of twice-daily dosing of SX-682, followed by combination of twice-daily dosed SX-682 and every 2-week Nivolumab (240 mg IV). Dose finding of SX-682 is performed using Bayesian optimal interval (BOIN) design to determine the maximum tolerated dose (MTD) when combined with Nivolumab. Pre-treatment and one on treatment (Day 28-35) biopsies are required for enrollment to evaluate change in tumor microenvironment immune cell composition by single cell-RNA sequencing, flow cytometry, RNA RT-qPCR, and IHC. The primary endpoint is to determine MTD; the key secondary endpoint is progression-free survival (PFS), defined as the time from enrollment to progression via iRECIST criteria or death. Nine of a planned 20 patients have been enrolled. Dose-level 1 (SX-682 50 mg BID) completed enrollment without dose-limiting toxicity (DLT). Dose-level 2, which commenced in June 2021, (SX-682 100 mg BID) is without DLTs, but has not completed enrollment at time of abstract submission. Nywening TM, Belt BA, Cullinan DR, et al. Targeting both tumour-associated CXCR2(+) neutrophils and CCR2(+) macrophages disrupts myeloid recruitment and improves chemotherapeutic responses in pancreatic ductal adenocarcinoma. 1) *Gut.* 2018;67(6):1112-1123.Steele CW, Karim SA, Leach JDG, et al. CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. 2) *Cancer Cell.* 2016;29(6):832-845. Clinical trial information: NCT04477343. Research Sponsor: U.S. National Institutes of Health., Bristol-Myers Squibb and Syntrix Pharmaceuticals provided Drug.

TPS632 **Trials in Progress Poster Session**

Phase 1b study of vactosertib in combination with nal-IRI plus 5FU/LV in patients with metastatic pancreatic ductal adenocarcinoma who have failed first-line gemcitabine/*nab*-paclitaxel.

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive malignancies and the leading cause of cancer-related death in the world, although recent advances in chemotherapies for metastatic PDAC provide better clinical outcomes. TGF-β is strongly involved in the tumor microenvironment of PDAC, and dysregulation of TGF-β signaling is a frequent molecular disturbance in PDAC progression and metastasis. Vactosertib is an orally bioavailable TGF-β signaling inhibitor that targets the TGF-β type I receptor kinase. In *in vivo* studies, vactosertib reduces cancer cell migration, invasion, and metastasis of various cancers, and combination of vactosertib with nal-IRI/5-FU/LV improves pancreatic cancer survival by suppressing cell migration, invasion, and epithelial-mesenchymal transition (EMT), highlighting a potential clinical application of this approach for PDAC patients (Hong et al, 2020). Based on this preclinical study, we develop a phase 1b study to determine the recommended phase 2 dose (RP2D) and to evaluate the safety of vactosertib in combination with nal-IRI/5FU/LV in patients with metastatic PDAC who have failed first-line gemcitabine/*nab*-paclitaxel. **Methods:** Eligible patients have histologically confirmed PDAC who have failed first-line gemcitabine/*nab*-paclitaxel with adequate organ function and performance status. This study is composed of two parts; dose escalation and dose expansion. In the dose escalation part (phase 1b), different dose levels of vactosertib (100 mg bid, 200 mg bid, and 300 mg bid) for escalation will be tested, starting with dose level 0 (DL 0, 200 mg bid) with 3 to 6 subjects recruited in each cohort. DL -1 is only tested when DL 0 is unacceptable. In the dose expansion part, one or two additional backfill cohorts among DL -1 through DL 2 will be opened for determination of the final RP2D. For each cohort, a maximum of 12 patients can be enrolled including the dose escalation and dose expansion phase. Patients in each cohort will receive vactosertib 100-300 mg orally twice per day 1-5 & day 8-12 with nal-IRI 70mg/m^2 intravenously day 1, LV 400mg/m^2 IV day 1, and continuous 5-FU 2400mg/m^2 infusion over 48 hours every 2 weeks. The primary endpoint is to determine RP2D and to evaluate safety of this combination. The key secondary endpoints are progression free survival, overall response rate, disease control rate based on RECIST 1.1 and overall survival. As of September 2021, 5 patients have been enrolled in DL 0 and 1 DLT has been reported in DL 0. This study is prospectively registered on ClinicalTrials.gov, NCT04258072. Clinical trial information: NCT04258072. Research Sponsor: MedPacto, Servier.

TPS633   **Trials in Progress Poster Session**

Phase I study of mesenchymal stem cell (MSC)-derived exosomes with KRAS^{G12D} siRNA in patients with metastatic pancreatic cancer harboring a KRAS^{G12D} mutation.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with few effective therapeutic options. Over 90% of patients with PDAC harbor activating mutations in *KRAS*, a known oncogenic driver of tumor growth, cancer cell survival and metastasis thus making for an attractive therapeutic target. However, targeting the most common KRAS mutations in pancreatic cancer (KRAS^{G12D} and KRAS^{G12V}) remains a pharmacological challenge. Exosomes are extracellular nanovesicles that are efficiently internalized by target cells and are under investigation as a drug-delivery vehicle for various therapeutic payloads, including nucleic acids such as small interfering RNA (siRNA). Previously published pre-clinical data demonstrate effective delivery of exosomes loaded with siRNA targeting KRAS^{G12D} leading to tumor control in various murine models of PDAC. **Methods:** This is a single arm, single institution, phase I trial evaluating treatment with KRAS^{G12D}-siRNA loaded exosomes. Large-scale production of KRAS^{G12D}-siRNA loaded exosomes from mesenchymal stromal cells will be performed at the MD Anderson Cancer Center using pre-specified GMP-compliant protocols. The primary endpoints of this study are to determine a maximum tolerated dose (MTD) of KRAS^{G12D}-loaded exosomes and to identify dose-limiting toxicities (DLT). Key secondary endpoints include the pharmacokinetics of circulating exosomes, overall response rate, disease control rate (defined as partial responses and patients with stable disease), median progression-free survival (PFS) and median overall survival (OS). Key inclusion criteria include histologically confirmed metastatic pancreatic ductal adenocarcinoma, documented progression on one or more lines of systemic therapy, and documented presence of a KRAS^{G12D} mutation. Selected correlative studies include measurement of circulating siRNA and KRAS^{G12D} DNA using PCR. This trial will enroll up to 28 patients and will follow a 3+3 design for dose escalation. This trial is actively accruing and has enrolled six patients at the time of submission. Clinical trial information: NCT03608631. Research Sponsor: U.S. National Institutes of Health.

TPS634   **Trials in Progress Poster Session**

Phase I study of hydroxychloroquine plus binimetinib in patients with metastatic pancreatic cancer (the HOPE trial).

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a devastating malignancy with a dearth of effective therapeutic options. Over 90% of PDAC harbor activating mutations in the KRAS oncoprotein, which in turn leads to activation of downstream effector proteins in the the RAF-MEK-ERK mitogen-activated protein kinase (MAPK) signaling cascade serving to promote tumor cell survival, growth and metastasis. Unfortunately, single agent treatment with MAPK-inhibitors have had limited therapeutic efficacy in patients with PDAC owing to development of various tumor-cell intrinsic resistance mechanisms, including upregulation of autophagy. Hydroxychloroquine is an antimalarial drug that functions to inhibit autophagy by inhibiting acidification of lysosomes. Previously published preclinical data suggest combination therapy with binimetinib, a MEK 1/2 inhibitor, and hydroxychloroquine leads to enhanced killing of PDAC cells *in vitro* and *in vivo*. **Methods:** This is a single arm, single center phase I trial of binimetinib plus hydroxychloroquine in patients with metastatic pancreatic cancer harboring a KRAS mutation. All patients will receive binimetinib at a fixed dose of 45mg PO twice daily (14-day cycles) while hydroxychloroquine will be dosed at 400mg PO twice daily (14-day cycles) and dose escalated using a Bayesian optimal interval design with a target toxicity rate of 0.3. Key eligibility criteria include histologically confirmed metastatic pancreatic adenocarcinoma, prior treatment with at least one line of systemic therapy and a documented KRAS mutation. An estimated 24 patients will be enrolled in the first phase of this study and up to 15 patients in the dose expansion cohort. The primary endpoint of this study is to determine the maximum tolerated dose (MTD) of hydroxychloroquine when combined with a fixed dose of binimetinib. Key secondary endpoints include safety and toxicity profile, response rate, progression free survival (PFS) and overall survival (OS). This study is ongoing and has enrolled 10 patients at the time of submission. Clinical trial information: NCT04132505. Research Sponsor: U.S. National Institutes of Health., Pharmaceutical/Biotech Company.

TPS635   **Trials in Progress Poster Session**

PASS-01: Pancreatic adenocarcinoma signature stratification for treatment–01.

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Background: Over 70% of patients with pancreatic ductal adenocarcinoma (PDAC) present with metastatic disease where the mainstay of treatment is combination chemotherapy. Two pivotal phase III trials showed survival benefit of mFOLFIRINOX (mFFX) and gemcitabine/nab-paclitaxel (GnP), respectively, compared to gemcitabine alone. Both are considered standard 1st line treatment options but have not been compared prospectively. Other than the BRCA phenotype there are no predictive molecular markers to identify which patients will benefit from mFFX versus GnP. Growing data suggests that RNA signatures and GATA6 expression may predict response to chemotherapy. Genomic platforms do identify small subsets of patients who may benefit from a targeted approach however, impact has been small. Patient-derived organoids (PDOs) are now feasible to passage for drug pharmacotyping that could inform drug therapy approaches. Combining all molecular strategies in real time including genomics, RNA signatures and adding PDO drug sensitivities could enable better precision choices for more patients with metastatic PDAC. **Methods:** PASS-01 is a multi-institutional randomized phase II trial evaluating the benefit of 1st line mFFX vs GnP in de novo metastatic PDAC patients with good PS who have undergone baseline tumor biopsies with tissue prepared for whole genome (WGS) and RNA sequencing and PDO generation/pharmacotyping using standard and novel drugs. The 1^O objective is to determine the PFS benefit of mFFX compared to GnP as 1st line treatment with 80% power to detect a median PFS of 7 vs 5 months, favoring mFFX. 27 of a planned 150 patients have been accrued to date. Secondary endpoints include ORR (RECIST), DOR, OS by chemotherapy and biomarkers of therapy response including GATA-6 as a surrogate biomarker for the Moffit RNA classifier. Exploratory objectives include: to evaluate if each PDO DNA/RNA signature matches the patient and if the PDO chemotherapy sensitivities correlate to the patient's 1st line response; to evaluate the benefit in switching patients to 2nd line treatment based on PDO drug sensitivity; to evaluate novel agents derived from PDO pharmacotyping and potential findings from profiling in 2nd/3rd line treatment; to explore retrospectively whether serial cell-free circulating tumor DNA analysis, circulating tumor cells and CA19.9 could reflect potential early predictors of emerging or de novo resistance and explore biomarkers of immune-oncologic sensitivity with multiplex immunohistochemistry. Each patient's WGS and PDO data is discussed at a combined tumor board with study investigators immediately following their 1st 8-week CT and ongoing as data develops with the goal of recommending precision treatment choices back to their treating investigator. References: Conroy T et al. NEJM, 2011.; Von Hoff DD et al. NEJM,2013; Aung KL et al. CCR 2017; O'Kane G et al. CCR 2019; Tiriac H et al. Can Discov, 2018. Clinical trial information: NCT04469556. Research Sponsor: Stand Up 2 Cancer, Lustgarten Foundation, Pancreatic Cancer Canada, Ontario Institute of Cancer Research.

TPS636   **Trials in Progress Poster Session**

A phase I study of first-line L-glutamine (Gln) with gemcitabine (gem) and nab-paclitaxel (nab-p) in advanced pancreatic cancer (GlutaPanc).

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Background: Cytotoxic chemotherapy remains the preferred first-line treatment for advanced or unresectable pancreatic cancer with combination regimens including 5-fluoruracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), or gem and nab-p. The use and response of second- and third-line therapies remains dismal, thus the optimization of first-line treatment is critical. Our previous work investigating Gln metabolism in pancreatic ductal adenocarcinoma (PDAC) through glutaminase inhibition indicates that Gln deprivation in PDAC increases cancer cell survival and resistance to chemotherapy. However, when PDAC cell were treated with Gln supplementation, there was an increase in PDAC cell death with increasing concentrations of gem. In this present study we aim to test the feasibility and safety of combining L-Gln with gem and nab-p in treatment-naïve patients with unresectable or metastatic PDAC. **Methods:** This is a single arm, single center, phase I study. The primary objective is to assess the recommended phase II dose (RP2D) of L-Gln in combination with gem and nab-p. The RP2D will be assessed by escalation of overdose control (EWOC), an adaptive Bayesian design, through determination of the maximum tolerated dose (MTD) across 3 doses of gem, nab-p, and L-Gln. The MTD is defined as the dose such that the probability of dose-limiting toxicities (DLTs) at the MTD is $\theta = 0.33$. The first patient will receive 1000 mg/m^2 gem, 125 mg/m^2 nab-p, and 0.1 g/kg L-Gln and the subsequent doses will be determined by the EWOC algorithm. We plan to enroll a maximum of 16 patients. L-Gln is administered orally BID throughout the 28-day cycle with a one-week lead-in prior to the beginning of the first cycle where gem and nab-p are administered on days 1, 8, and 15 of each cycle. Key inclusion criteria include: advanced or unresectable, histologically confirmed pancreatic cancer that is either new or recurrent (if recurrent, prior neoadjuvant or adjuvant chemotherapy or chemoradiation is allowed but must have been completed >12 months prior to recurrence), ECOG PS ≤ 2 or KP ≥ 60%, and normal organ and marrow function. Secondary objectives are to describe any preliminary evidence of antitumor activity by assessment of objective response rate, progression-free survival, and overall survival. Since October 2020, 3 patients have been screened and 3 enrolled. Clinical trial information: NCT04634539. Research Sponsor: Cedars-Sinai Medical Center.

TPS637   **Trials in Progress Poster Session**

Randomized phase II trial of two different nutritional approaches for patients receiving treatment for their advanced pancreatic cancer.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is characterized by stromal fibrosis, hypoxia, and nutritional deprivation. PDAC tumors grow aggressively, diagnosis is typically made after metastasis and the disease remains associated with poor outcomes. The triplet chemotherapy regimen of gemcitabine, nab-paclitaxel with cisplatin was associated with a median overall survival of 16.4 months in patients with metastatic pancreatic cancer in the first-line setting (Jameson et al., 2020). Nutritional, metabolic interventions offer an opportunity to fundamentally change the tumor microenvironment and improve outcomes for patients. A ketogenic diet defined as lower carbohydrate, lower protein, and higher fat can significantly reduce glucose and insulin and increase metabolically active ketone bodies and has been evaluated in patients with a variety of solid tumors (Weber et al, 2020). Recently, a ketogenic diet combined with triplet chemotherapy was shown to inhibit murine pancreatic KPC tumor growth and significantly prolong animal survival over chemotherapy alone. Tumor growth inhibition was associated with glucose depletion, altered TCA substrate usage, and NADH elevation. **Methods:** In this Phase II randomized clinical trial (NCT04631445), we are evaluating a medically supervised ketogenic diet (MSKD) versus a standard diet when combined with the triplet therapy in patients with treatment-naive advanced pancreatic cancer. The primary endpoint is progression free survival for triplet therapy while on MSKD or non-MSKD. Secondary endpoints include disease control rate (PR+ CR+ SD for at least 9 weeks), change in CA 19-9 (or CA125, or CEA if not expressers of CA 19-9), average insulin levels, HbA1c, body weight, a comparison of gut microbial diversity, changes in serum metabolites and quality of life via the EORTC QLQ-C30 assessment. Unlike prior ketogenic intervention studies, the MSKD is being supported by a continuous care nutrition intervention through Virta Health Corp, that offers tracking of daily ketone and glucose levels, a web-based software application, education, and communication with a remote care team to ensure sustained nutritional ketosis. A total of 40 patients with untreated metastatic PDAC are planned for enrollment, 20 randomized to each arm. The trial opened for accrual November 2020. Clinical trial information: NCT04631445. Research Sponsor: Patient advocates.

TPS638   **Trials in Progress Poster Session**

GATA6 Expression as a predictor of response to perioperative chemotherapy in resectable pancreatic adenocarcinoma: A multicenter Canadian phase II study (NeoPancONE).

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Background: Prospective studies of the benefit of neoadjuvant chemotherapy in resectable pancreatic adenocarcinoma (PDAC) have been reported. The ideal peri-operative regimen is yet to be determined. Adjuvant FOLFIRINOX (mFFX) in resected PDAC has been proven to improve overall survival (OS) relative to adjuvant gemcitabine. An accepted perioperative approach involves delivering the majority of chemotherapy (6-8 cycles) in the pre-operative setting, while the remainder (of 12 cycles) is administered post-operatively. This pre-operative treatment period may allow for chemosensitivity assessment, and better patient selection for surgery, thereby improving R0 resection rates and reducing the frequency of early post-operative recurrence. Data from the COMPASS trial (NCT02750657) has shown that shown that low levels of the transcription factor GATA6 expression is a putative surrogate for the RNA Moffit signature and predictive of a chemoresistant phenotype in advanced PDAC. NeoPancONE will evaluate clinical outcomes and molecular biomarkers including GATA6 and radiomic biomarkers in pts with resectable PDAC treated with perioperative mFFX. **Methods:** NeoPancONE is a Phase 2, open-label, single arm study in pts with resectable PDAC. Tissue and serum are collected for biomarker testing, including GATA6 by FISH and IHC (1) with expression levels measured by RNAseq, and longitudinal ctDNA analysis. Pts with histologically confirmed, resectable PDAC and ECOG PS 0-1 will be recruited over 2.5 years. Resectability will be determined by central review as per NCCN guidelines. The primary objective is to evaluate disease-free survival in resectable PDAC treated with peri-operative mFFX according to baseline tumor GATA6 expression level. The ratio of GATA6-high to low is expected to be approximately 4:1[1]. Assuming 1-year disease-free survival of 65% in the GATA6-high, compared to 34% in the GATA6-low cohort, this corresponds to a hazard ratio of 2.5. With 80% power and a 5% 2-sided significance level, a total of 84 patients will be enrolled with 67 events expected in the GATA6 high cohort and 17 in GATA6 low. Participants will receive up to 6 cycles of neoadjuvant mFFX. After neoadjuvant chemotherapy, definitive surgical resection will proceed as deemed appropriate by a hepatobiliary surgeon. Post-operatively, pts will receive up to 6 cycles of adjuvant chemotherapy. Secondary objectives include determination of overall response rate, incidence of R0 resection, OS, Moffit gene expression profiling (RNAseq), ctDNA, and radiomic signatures to predict outcomes. Enrolment for NeoPancONE began in October 2020 and is being conducted at 8 sites across Canada. To date, 23 pts have been recruited. The study duration will be five years. Reference: O'Kane G M et al. Clin Can Res Sep 2020. Clinical trial information: NCT04472910. Research Sponsor: Pancreatic Cancer Canada.

TPS639   **Trials in Progress Poster Session**

Biomarker-oriented study of pembrolizumab in combination with chemotherapy in chemotherapy-naïve advanced pancreatic cancer: A phase 2 trial-in-progress.

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Background: Pancreatic cancer (PC) is well-known as a strongly immunosuppressive tumor. The tumor microenvironment of PC play a fundamental part in maintaining a non-immunogenic and immuno-suppressive environment through the production of inhibitory cytokines and complex interaction between tumor cells, regulatory T cells, and myeloid-derived suppressor cells (Li KY et al. 2020). However, through integrated genomics and immunophenotyping, the immune-rich type had a relatively good prognosis in advanced PC (Wartenberg M et al. 2018). Based on this, various attempts have been made to apply immune checkpoint inhibitor (ICI) to PC. Disappointingly, ICI monotherapy is ineffective in most advanced PCs, and a strategy of combining ICI with ICI, chemotherapy or targeted therapy has been recently tried. However, the mechanism of immune modulation induced by ICI in combination with chemotherapy in PC is still not well-known, so biomarker studies are needed to understand the role of immunotherapy in advanced PC. Also based on this, it is expected to develop an effective ICI treatment strategy in PC. This study is a non-randomized, parallel assignment phase 2 trial aimed to explore dynamic modulation of the immune system caused by co-administration of pembrolizumab and cytotoxic chemotherapy in patients with advanced PC. **Methods:** Eligible patients have recurred or metastatic pancreatic cancer. Patients who have received chemotherapy for advanced PC are excluded, except for previous adjuvant chemotherapy. Patients who have received ICI are excluded. There are 2 chemotherapy cohorts (FOLFIRINOX, n=41; Gemcitabine/Nab-paclitaxel, n=36). Patients enrolled in the FOLFIRINOX cohort will receive pembrolizumab 200mg intravenously once every 3 weeks, plus FOLFIRINOX chemotherapy every 2 weeks. In Gemcitabine/Nab-paclitaxel cohort, patients will receive gemcitabine 1000mg/m2 plus nab-paclitaxel 125mg/m2 day 1, 8, 15 of a 4-week cycle, plus pembrolizumab 200mg intravenously once every 3 weeks. The primary endpoint is objective response rate, with key secondary endpoints including progression-free survival, duration of response, disease control rate, overall survival, safety, and patient-reported outcome. For evaluating metabolic response, ^{18}F-FDG PET-CT scan will be conducted before treatment and at the first response evaluation. Tumor tissue biopsies are performed three times in total: screening, the first response evaluation, and disease progression. Blood samples are being collected every cycles for translational biomarker studies. Clinical trial information: NCT04447092. Research Sponsor: None.

TPS640   **Trials in Progress Poster Session**

Optimizing pancreatic cancer management with next generation imaging and liquid biopsy (CHANGE-PDAC).

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Background: Pancreatic ductal adenocarcinoma (PDAC) is anticipated to become the second-leading cause of cancer-related deaths by 2030. Systemic therapy remains the mainstay of treatment for those with unresectable/metastatic disease. There is an urgent need for biomarkers to rapidly assess treatment response to spare patients from the significant toxicities and costs of an ineffective regimen, and to guide decision-making for a therapeutic switch with a higher chance of efficacy. Circulating tumor (ct)DNA and PET/MRI represent promising emerging biomarkers for early response prediction. This is a prospective non-randomized study examining the role of ctDNA and PET/MRI in adjudicating early treatment response among patients with unresectable locally advanced or metastatic PDAC receiving systemic therapy. **Methods:** Approximately 158 patients with advanced PDAC will be recruited at the time of initiation of a new line of treatment in either the first or later-line setting. Patients receiving both standard of care and/or experimental therapies are permitted to enroll. Research blood samples will be collected at pre-treatment, 48 hours, two weeks, one month, and two months after treatment start for analysis of mutant ctDNA (using the FoundationOne/Natera platform). PET/MRI will be performed at pre-treatment and 4 weeks post treatment. All patients must have an ECOG performance status of 0-2 and have radiographically measurable disease. Clinical data will be collected prospectively, including demographics, ECOG performance status, CA 19-9 levels, chemotherapy type and dose intensity, and clinical and radiographic assessment of treatment response using RECIST 1.1 criteria. Enrollment began in August 2021. The primary endpoint is the correlation between change in tumor-derived ctDNA with radiographic progression, as measured by the change in tumor size. The Wilcoxon rank sum test will be used to compare the change in ctDNA with treatment between response vs. resistance. Cox proportional hazard regression modelling will be used to correlate the change in ctDNA with progression-free survival and overall survival. Secondary endpoints include defining thresholds for early chemotherapy switch using dynamic and quantitative changes in ctDNA and PET/MRI biomarkers for use in future prospective trials, establishing the relationship between early changes in PET/MRI and treatment response/resistance, and developing a multivariable model combining ctDNA and PET/MRI biomarkers to predict treatment response/resistance. Research Sponsor: U.S. National Institutes of Health.