ATTRACTION-5: A phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III (pStage III) gastric or gastroesophageal junction (G/GEJ) cancer.

Masanori Terashima, Yoon-Koo Kang, Young-Woo Kim, Narikazu Boku, Hyun Cheol Cheol Chung, Jen-Shi Chen, Jiafu Ji, Ta-Sen Yeh, Li-Tzong Chen, Min-Hee Ryu, Jong Gwang Kim, Takeshi Omori, Sun Young Rha, Tae-Yong Kim, Keun Won Ryu, Shinichi Sakuramoto, Yasunori Nishida, Norimasa Fukushima, Takanobu Yamada, Mitsuru Sasako; Shizuoka Cancer Center, Division of Gastric Surgery, Nagaizumi, Japan; Asan Medical Center, Seoul, Korea, Republic of (South); National Cancer Center, Goyang-Si, Korea, Republic of (South); The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Linkou Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; Beijing Cancer Hospital, Beijing, China; Chang Gung Memorial Hospital, Taoyuan, Taiwan; Department of Oncology, National Cheng Kung University Hospital, and Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan; Kyungpook National University, Daegu, South Korea; Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan; Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea, Republic of (South); Seoul National University Hospital, Jongno-Gu, South Korea; National Cancer Center, Goyang-Si, South Korea; Saitama Medical University International Medical Center, Hidaka, Japan; Keiyukai Sapporo Hospital, Sapporo, Japan; Department of Urology, Yamagata Prefectural Central Hospital, Yamagata-Shi, Japan; Kanagawa Cancer Center, Yokohama, Japan; Yokohama Christian Hospital, Higashiyodogawa-Ku, Japan

Background: Nivolumab plus chemotherapy (N+C) in the first-line treatment and nivolumab monotherapy in the third- or later-line have shown survival benefit in patients with unresectable advanced or recurrent G/GEJ cancer. Adjuvant chemotherapy after D2 or more extended gastrectomy is a widely used standard of care for pStage III G/GEJ cancer in Asia. However, standard adjuvant chemotherapy has shown limited efficacy for pStage III G/GEJ cancer. ATTRACTION-5 is the first phase 3 study to evaluate an immune checkpoint inhibitor in combination with adjuvant chemotherapy for pStage III G/GEJ cancer. Here, we report the first confirmatory results of N+C as postoperative adjuvant treatment.

Methods: The ATTRACTION-5 study is a multicenter, double-blind, randomized study conducted in Japan, Korea, Taiwan, and China. We enrolled patients with pStage III G/GEJ cancer who had undergone D2 or more extended gastrectomy. Investigators selected an appropriate adjuvant chemotherapy (tegafur/gimeracil/oteracil [S-1] therapy or capecitabine plus oxaliplatin [CapeOX] therapy) for each patient, and thereafter patients were randomly assigned (1:1) to the N+C or placebo plus chemotherapy (P+C) arm, using the allocation factors of country and disease stage. The primary endpoint was centrally-assessed relapse-free survival (RFS). The sample size was calculated, based on the results of the ACTS-GC study and the CLASSIC study (The assumed hazard ratio [HR], 0.67; the assumed 3-year RFS, 71% vs 60%). Secondary endpoints were investigator-assessed RFS, overall survival (OS), and 3-year RFS and OS rates.

Results: A total of 755 patients underwent randomization from February 2017 to August 2019: 377 were assigned to the N+C arm and 378 to the P+C arm. The final analysis of RFS was performed based on the clinical data cutoff of August 2022, with the minimum follow-up of 36 months after the last patient was randomized. The primary efficacy endpoint of centrally-assessed RFS was not met (HR, 0.90; 95.72% CI, 0.69–1.18; P=0.4363), with the 3-year RFS rates of 68.4% (95% CI, 63.0–73.2) in the N+C arm and 65.3% (95% CI, 59.9–70.2) in the P+C arm. The completion rate of the planned postoperative adjuvant treatment was 61.5% in the N+C arm and 71.4% in the P+C arm. Incidences of grade=3 TRAEs, serious TRAEs, and TRAEs leading to discontinuation were 54.4%, 25.3%, and 9.2%, respectively, in the N+C arm and 46.8%, 10.7%, and 3.5% in the P+C arm.

Conclusions: The ATTRACTION-5 study of N+C vs P+C in patients with pStage III G/GEJ cancer after D2 or more extended gastrectomy did not meet the primary endpoint of RFS. The safety profile in the ATTRACTION-5 study was consistent with its known safety profile. Clinical trial information: NCT03006705. Research Sponsor: ONO Pharmaceutical; Bristol Myers Squibb.
Perioperative PD-1 antibody toripalimab plus SOX or XELOX chemotherapy versus SOX or XELOX alone for locally advanced gastric or gastro-oesophageal junction cancer: Results from a prospective, randomized, open-label, phase II trial.

Shuqiang Yuan, Run-Cong Nie, Ying Jin, Cheng-cai Liang, Rui Jian, Yuan-fang Li, Haibo Qiu, Wei Wang, Shi Chen, Dong-sheng Zhang, Chun-yu Huang, Yi-hong Ling, Qiu-xia Yang, Zi-Xian Wang, Wen-long Guan, Ying-bo Chen, Xiao-wei Sun, Zhi-wei Zhou, Feng Wang, Rui-Hua Xu; State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, Guangdong, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China; The 6th Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: The combination of PD-1 antibody and chemotherapy was shown to be effective in advanced gastric or gastro-oesophageal junction (GEJ) cancer, but has not yet been investigated in the context of locally advanced patients. In this study, we conducted a prospective, randomized, open-label phase II trial to evaluate the effectiveness of adding PD-1 antibody to perioperative chemotherapy in patients with locally advanced resectable gastric or GEJ cancer. Methods: In this randomized, open-label, phase II study, patients with resectable gastric or GEJ cancer clinically staged as cT3-4a N+M0 were randomized (1:1) to three preoperative and five postoperative 3-week cycles of SOX/XELOX (C arm) or PD-1 antibody toripalimab plus SOX/XELOX, followed by toripalimab monotherapy for 6 months (C+T arm). The primary endpoint was pathological complete regression/moderate regression rate (TRG 0/1). The secondary endpoints were pathological complete response (pCR), R0 resection rate, recurrence-free survival, event-free survival, objective response rate, disease control rate, overall survival and treatment safety. The study had been completed enrollment, and here, we analyzed the primary endpoint. Mantel-Haenszel test was used to test the difference of pathological regression between the two arms. The trial was registered at ClinicalTrials.gov, identifier: NCT04250948. Results: Between Oct 2019 and June 2022, 108 patients (C+T arm, n=54; C arm, n=54) were enrolled and assessed using intention-to-treat analysis. Patients in the toripalimab plus chemotherapy arm achieved higher proportion of TRG 0/1 than those in the chemotherapy arm (44.4% [24/54, 95% CI: 30.9%-58.6%] vs 20.4% [11/54, 95% CI: 10.6%-33.5%]; P=0.009). A higher pCR rate was observed in the C+T arm (24.1% [13/54, 95% CI:13.5%-37.6%] vs 9.3% [5/54, 95% CI: 3.1%-20.3%]; P=0.039). Preoperative therapies (3 cycles) were completed in 96.3% of patients and postoperative cycles (>3 cycles) in 81.5%, with no significant differences observed between these two arms. A higher proportion of downstaging was observed in the C+T arm (ypT0-2: 46.3% vs 22.2% [P=0.002]; ypstage 0-1: 38.9% vs 16.7% [P=0.024]). Surgical morbidity (11.8% in the C+T arm vs 13.5% in the C arm) and mortality (1.9% vs 0%) and treatment-related grade 3-4 adverse events (27.8% vs 25.9%) were comparable between the arms. Conclusions: Perioperative PD-1 antibody toripalimab plus chemotherapy demonstrated a significantly improved pathological regression and might be a promising option for patients with locally advanced resectable gastric or GEJ cancer. Clinical trial information: NCT04250948. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.
Efficacy, safety and patient reported outcomes (PROs) from the phase III IMbrave050 trial of adjuvant atezolizumab (atezo) + bevacizumab (bev) vs active surveillance in patients with hepatocellular carcinoma (HCC) at high risk of disease recurrence following resection or ablation.

Masatoshi Kudo, Minshan Chen, Pierce K. H. Chow, Ahmed Omar Kaseb, Han Chu Lee, Adam C. Yopp, Lars Becker, Sairy Hernandez Painter, Bruno Kovic, Qinshu Lian, Ning Ma, Chun Wu, Shukui Qin, Ann-Lii Cheng; Kindai University Hospital, Osaka, Japan; Sun Yat-Sen University Cancer Center, Guangdong Province, China; National Cancer Centre of Singapore, Singapore, Singapore; MD Anderson Cancer Center, Houston, TX; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; UT Southwestern Medical Center, Dallas, TX; F. Hoffmann-La Roche, Basel, Switzerland; Genentech, Inc., South San Francisco, CA; Hoffmann-La Roche Limited, Mississauga, ON, Canada; Roche (China) Holding Ltd., Shanghai, China; Jinling Hospital of Nanjing University of Chinese Medicine, Nanjing, China; National Taiwan University Hospital, Taipei, Taiwan

Background: In IMbrave050, adjuvant atezo + bev demonstrated a statistically significant and clinically meaningful improvement in recurrence-free survival (RFS) vs active surveillance in patients (pts) at high risk of HCC recurrence following resection or ablation with curative intent. Further, the safety of atezo + bev was generally manageable. Here, we additionally report PRO data from IMbrave050.

Methods: IMbrave050 (NCT04102098) enrolled HCC pts at high risk of recurrence following resection or ablation. Pts were randomized to Arm A (atezo + bev) or Arm B (active surveillance). Pts in Arm A received atezo 1200 mg + bev 15 mg/kg IV q3w for a period of one year (17 cycles). Pts in Arm B underwent active surveillance for one year and were eligible to crossover to atezo + bev following independent review facility (IRF) confirmation of recurrence. The primary endpoint was IRF-assessed RFS. Pre-specified exploratory analyses included change from baseline in global health status (GHS)/quality of life (QoL), physical functioning, role functioning, emotional functioning, and social functioning. Clinically meaningful deterioration was defined as a ≥ 10-point decrease. Pts completed the IL42–EORTC QLQ-C30 (reduced) questionnaire at baseline and then at every odd treatment/surveillance visit through Cycle 17. Results: The ITT population included 334 pts in both Arms A and B. With a median follow-up time of 17.4 mo (clinical cutoff date: 21 Oct 2022), IRF-RFS HR was 0.72 (95% CI: 0.56, 0.93; P = 0.0120). In the safety population, Grade 3 or 4 adverse events occurred in 41% of 332 Arm A pts and 13% of 330 Arm B pts. In ITT pts, IL42 completion rates remained ≥ 93% in both arms from baseline through treatment/surveillance Cycle 17. Mean scores at baseline in both arms were high and similar, as measured by the GHS/QoL and physical, role, emotional and social functioning scales. Mean changes from baseline were not considerable through Cycle 17 and were similar between arms as evidenced by overlapping 95% CIs. Pts’ GHS/QoL and functioning was maintained through Cycle 17, with no clinically meaningful deterioration observed at any time. Conclusions: Statistically significant and clinically meaningful improvement in RFS was seen in pts receiving atezo + bev vs active surveillance. Atezo + bev safety was generally manageable, and consistent with the established safety profiles of each therapeutic agent and with the underlying disease. PRO outcome analyses revealed similar overall health-related QoL (HRQoL) and functioning between atezo + bev and active surveillance, and that treating high-risk pts with HCC with adjuvant atezo + bev following procedures with curative intent did not result in a clinically meaningful deterioration in HRQoL or function. Clinical trial information: NCT04102098. Research Sponsor: Roche.
Health-related quality of life (HRQoL) in the phase 3 KEYNOTE-966 study of pembrolizumab (pembro) plus gemcitabine and cisplatin (gem/cis) versus placebo plus gem/cis for advanced biliary tract cancer (BTC).

Changhoon Yoo, Richard S. Finn, Heinz-Josef Klümper, Robin Kate Kelley, Arndt Vogel, Junji Furuse, Zhenggang Ren, Thomas Yau, Stephen Lam Chan, Masato Ozaka, Sang Cheul Oh, Shanzhi Gu, Joon Oh Park, Juan W. Valle, Julien Edeline, Shital Kamble, Josephine M Norquist, Li Yu, Usha Malhotra, Makoto Ueno; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; University of California Los Angeles, Los Angeles, CA; Amsterdam University Medical Center, Amsterdam, Netherlands; University of California, San Francisco, CA; Hannover Medical School, Hannover, Germany; Kyorin University, Tokyo, Japan; Zhongshan Hospital, Fudan University, Shanghai, China; The University of Hong Kong, Hong Kong, China; Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China; The Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR), Tokyo, Japan; Korea University Guro Hospital, Seoul, Korea; Republic of (South); Hunan Cancer Hospital (The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University), Changsha, China; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom; Centre Eugène Marquis, Rennes, France; Merck & Co., Inc., Rahway, NJ; Kanagawa Cancer Center, Yokohama, Japan

Background: In the randomized, double-blind, phase 3 KEYNOTE-966 trial (N = 1069; NCT04003636), pembro + gem/cis significantly improved OS versus placebo + gem/cis (HR 0.83; 95% CI 0.72-0.95; P = 0.0034) and had an expected and manageable safety profile as first-line therapy for unresectable locally advanced or metastatic BTC. We present the protocol-specified exploratory patient-reported outcomes (PROs) from KEYNOTE-966. Methods: PROs were assessed using the EORTC QLQ-C30, EORTC QLQ-BIL21, and EQ-5D-5L questionnaires. The analysis population included all treated patients (pts) who completed ≥1 HRQoL assessment for the specific endpoint. A constrained longitudinal analysis model (covariates: treatment, time, treatment by time interaction, and stratification factors) was used to compare least squares mean (LSM) score changes from baseline (BL) to wk 18 (ie, latest timepoint that completion was ≥60% and compliance was ≥80%) in QLQ-C30 global health status (GHS)/QoL, physical functioning (PF), and role functioning (RF), QLQ-BIL21 jaundice and pain, and EQ-5D-5L visual analogue scale (VAS). A stratified Cox proportional hazards model was used to assess the magnitude of the between-arm difference in time to deterioration (TTD) in GHS/QoL, PF, RF, jaundice, and pain (ie, time to first onset of ≥10-point deterioration from BL in each scale/subscale confirmed by ≥10-point deterioration from BL at the next visit; established as clinically relevant). Results: Questionnaire compliance was >87% from BL to wk 18 in both arms. LSM changes from BL to wk 18 in QLQ-C30 GHS/QoL, PF, and RF, QLQ-BIL21 jaundice and pain, and EQ-5D-5L VAS were similar between arms. Time to deterioration was also similar between arms: median not reached (NR) vs 21.2 mo for GHS/QoL (HR 0.86, 95% CI 0.70-1.07), NR vs 12.0 mo for PF (HR 0.95, 95% CI 0.78-1.17), 6.5 mo vs 5.8 mo for RF (HR 0.98, 95% CI 0.81-1.18), NR vs NR for jaundice (HR 1.20, 95% CI 0.94-1.54), and NR vs NR for pain (HR 0.79, 95% CI 0.59-1.05). Conclusions: HRQoL was maintained when pembro was added to gem/cis. Together with the efficacy and safety data, these results support pembro + gem/cis as a new first-line treatment option for advanced BTC. Clinical trial information: NCT04003636. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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<tr>
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<th>Pembrol + Gem/Cis</th>
<th>Placebo + Gem/Cis</th>
<th>Difference in LS Means (95% CI)</th>
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<tr>
<td><strong>QLQ-C30</strong></td>
<td></td>
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<tr>
<td>GHS/QoL</td>
<td>n = 518</td>
<td>n = 517</td>
<td></td>
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<tr>
<td>Change from BL to wk 18</td>
<td>-2.5 (-4.5, -0.5)</td>
<td>-2.5 (-4.5, -0.5)</td>
<td>0.0 (-2.5, 2.6)</td>
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<tr>
<td>PF</td>
<td>-6.4 (-8.3, -4.5)</td>
<td>-7.7 (-9.6, -5.7)</td>
<td>1.2 (-1.4, 3.9)</td>
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<tr>
<td>RF</td>
<td>-7.0 (-9.6, -4.5)</td>
<td>-9.7 (-12.3, -7.1)</td>
<td>2.7 (-0.8, 6.1)</td>
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<tr>
<td><strong>QLQ-BIL21</strong></td>
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<tr>
<td>Jaundice</td>
<td>n = 518</td>
<td>n = 516</td>
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<tr>
<td>Change from BL to wk 18</td>
<td>1.1 (-1.1, 3.4)</td>
<td>0.1 (-1.1, 1.2)</td>
<td>0.3 (1.4, 1.9)</td>
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<tr>
<td>Pain</td>
<td>-5.9 (-7.8, -4.1)</td>
<td>-4.1 (-6.0, -2.2)</td>
<td>-1.9 (-4.3, 0.5)</td>
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<td><strong>EQ-5D-5L</strong></td>
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<tr>
<td>VAS</td>
<td>n = 518</td>
<td>n = 517</td>
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<tr>
<td>Change from BL to wk 18</td>
<td>-3.4 (-5.2, -1.7)</td>
<td>-3.6 (-5.3, -1.8)</td>
<td>0.1 (-2.2, 2.5)</td>
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Higher GHS/QoL and functioning scores indicate improvement. Lower symptom scores indicate improvement.
Outcomes by occurrence of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC).

George Lau, Ann-Lii Cheng, Bruno Sangro, Masatoshi Kudo, Robin Kate Kelley, Won Young Tak, Antonio Gabbarini, Maria Reig, Ho Yeong Lim, David Tougeron, Enrico N. De Toni, Vincent C. Tam, Kabir Mody, Jun Gong, Carrie L. McCoy, Charu Gupta, Mallory Makowsky, Alejandra Negro, Ghassan K. Abou-Alfa; Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong Special Administrative Region, China; National Taiwan University Cancer Center, National Taiwan University Hospital, Taipei, Taiwan; Liver Unit and HPB Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain; Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, South Korea; Fondazione Policlinico Universitario Gemelli IRCCS, Universita' Cattolica del Sacro Cuore, Rome, Italy; Barcelona Clinic Liver Cancer, Hospital Clinic de Barcelona, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain; Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea; Department of Gastroenterology, Poitiers University Hospital, Poitiers, France; Department of Medicine II, University Hospital, LMU Munich, Munich, Germany; Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; Division of Hematology/Oncology, Department of Medicine, Mayo Clinic, Jacksonville, FL; Department of Medicine, Division of Hematology and Oncology, Cedars-Sinai Medical Center, Los Angeles, CA; AstraZeneca, Gaithersburg, MD; AstraZeneca, Wilmington, DE; Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Medical College, Cornell University, New York, NY

Background: Immune checkpoint inhibitor (ICI) studies have shown an association between the occurrence of imAEs and outcomes. In the Phase 3 HIMALAYA study (NCT03298451) in uHCC, STRIDE (Single T Regular Interval D) significantly improved overall survival (OS) vs sorafenib (S), and D monotherapy was noninferior to S. STRIDE and D had manageable safety (Abou-Alfa et al. NEJM Evid 2022). STRIDE is approved for uHCC in the United States and Japan and recommended for approval by the European Medicines Agency; D is approved in Japan. This exploratory analysis assessed the association between imAEs and outcomes in HIMALAYA. Methods: Safety was assessed in participants (pts) who received ≥1 dose of STRIDE (T 300 mg [one dose] plus D 1500 mg once every 4 weeks [Q4W]) or D (1500 mg Q4W). imAEs were AEs of special interest associated with drug exposure and consistent with an immune-mediated mechanism of action with no found alternate etiology. Median OS (mOS) and OS rates were estimated using the Kaplan–Meier method. OS hazard ratios (HRs) and 95% CIs were calculated using Cox modeling, with imAEs as a time-varying covariate and stratified by etiology (HBV/HCV/others), ECOG (0/1), and macro-vascular invasion (yes/no) for pts with vs without imAEs of any grade. Pts with >1 imAE were counted once. Results: In total, 388 pts (STRIDE) and 388 pts (D) were included in the analysis. Any grade imAEs, Grade 3 or 4 imAEs, and imAEs leading to discontinuation occurred in 139 (35.8%), 49 (12.6%), and 22 (5.7%) pts, respectively for STRIDE and 64 (16.5%), 25 (6.4%), and 10 (2.6%) pts, respectively for D. imAEs requiring high-dose steroids ($\geq$40 mg prednisone or equivalent daily) occurred in 78 (20.1%) pts for STRIDE and 37 (9.5%) pts for D. An improvement in OS was seen with STRIDE in pts with imAEs vs pts without (HR, 0.73; 95% CI, 0.56–0.95). OS rates at 6, 12, and 24 months (mo) were higher for STRIDE in pts with imAEs vs pts without. The association between imAEs and OS was less clear for D and may be limited by small pt number. In a landmark analysis of pts with vs without imAEs within 6 mo of STRIDE (n=307) or D (n=287), OS HRs (95% CIs) were 0.65 (0.47–0.90) and 1.39 (0.95–2.04), respectively. Conclusions: In HIMALAYA, imAEs with STRIDE or D were manageable and generally low grade. In this exploratory analysis, the occurrence of imAEs was associated with improved OS for STRIDE, generally consistent with findings for other ICIs. Clinical trial information: NCT03298451. Research Sponsor: AstraZeneca.
Short-course neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer: A multicenter randomized phase-II trial (NORPACT-1).

Knut Jørgen Labori, Svein Olav Bratlie, Christina Biørserud, Bergthor Björnsson, Erling Bringeland, Nils Elander, Jon Erik Grønbech, Johan Haux, Oskar Hemmingsson, Linn Nymo, Per Pfeiffer, Ville Sallinen, Ernesto Sparrelid, Kjetil Søreide, Bobby Tingstedt, Caroline Verbeke, Leif Klint, Svein Dueland, Kristoffer Lassen; Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden; Institute of Clinical Sciences, Department of Surgery, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Department of Surgery, Linköping University Hospital and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden; Department of Gastrointestinal Surgery, St. Olavs Hospital, Trondheim, Norway; Department of Biomedical and Clinical Sciences, Linköping University and Clatterbridge Cancer Centre NHS FT, Liverpool, Linköping, Sweden; Department of Oncology, Skaraborg Hospital Skövde and School of Health Sciences, University of Skövde, Skövde, Sweden; Department of Surgical and Perioperative Sciences, Surgery, Umeå University, Umeå, Sweden; Department of Gastrointestinal Surgery, University Hospital of North Norway, Tromsø, Norway; Odense University Hospital, Odense, Denmark; Gastroenterological Surgery/Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; Division of Surgery and Oncology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, Norway; Department of Surgery, Skåne University Hospital, Lund University, Lund, Sweden; Department of Pathology, Oslo University Hospital, Oslo, Norway; Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; Department of Oncology, Oslo University Hospital, Oslo, Norway; Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Oslo, Norway

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the Journal of Clinical Oncology.
Liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): 12- and 18-month survival rates from the phase 3 NAPOLI 3 trial.

Eileen Mary O’Reilly, Davide Melisi, Teresa Macarulla, Roberto A. Pazo Cid, Sreenivasa R Chandana, Christelle De La Fouchardiere, Andrew Peter Dean, Igor Kiss, Woo Jin Lee, Thorsten Oliver Goetze, Eric Van Cutsem, Scott Paulson, Tanios S. Bekaii-Saab, Shubham Pant, Richard Hubner, Zhimin Xiao, Huanyu Chen, Fawzi Benzaghrou, Zev A. Wainberg; Memorial Sloan Kettering Cancer Center, New York, NY; Investigational Cancer Therapeutics Clinical Unit and Section of Oncology, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology, Barcelona, Spain; Hospital Universitario Miguel Servet, Zaragoza, Spain; Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI; Centre Léon Bérard, Lyon, France; St. John of God Hospital Subiaco, Subiaco, Australia; Masaryk Memorial Cancer Institute, Brno, Czech Republic; Research Institute and Hospital, National Cancer Center, Goyang, South Korea; Krankenhaus Nordwest, University Cancer Center Frankfurt and Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt, Germany; University Hospital Leuven (UZ Leuven), Leuven, Belgium; Texas Oncology - Baylor Charles A. Sammons Cancer Center, Dallas, TX; Mayo Clinic Cancer Center Scottsdale, Phoenix, AZ; The University of Texas MD Anderson Cancer Center, Houston, TX; Medical Oncology Department, The Christie NHS Foundation Trust, Manchester, UK, Manchester, United Kingdom; Ipsen, Cambridge, MA; IPSEN, Cambridge, MA; Department of Medicine, Division of Hematology and Oncology, University of California at Los Angeles, Los Angeles, CA

Background: Liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA and Europe for mPDAC following progression with gemcitabine-based therapy. A phase 1/2 study (NCT02551991) demonstrated promising anti-tumor activity in patients with mPDAC who received first-line liposomal irinotecan 50 mg/m² + 5-FU 2400 mg/m² + LV 400 mg/m² + oxaliplatin 60 mg/m² (NALIRIFOX). Here, we present results from NAPOLI 3 (NCT04083235), a randomized, open-label, phase 3 study investigating the efficacy and safety of NALIRIFOX compared with nab-paclitaxel 125 mg/m² + gemcitabine 1000 mg/m² (Gem+NabP) as first-line therapy in patients with mPDAC.

Methods: Eligible patients with histopathologically/cytologically confirmed untreated mPDAC were randomized (1:1; stratified by Eastern Cooperative Oncology Group [ECOG] performance status, geographic region and presence/absence of liver metastases) to receive NALIRIFOX on days 1 and 15 of a 28-day cycle or Gem+NabP on days 1, 8 and 15 of a 28-day cycle. The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS), overall response rate (ORR) and safety. OS was evaluated when at least 543 events were observed using a stratified log-rank test with an overall one-sided significance level of 0.025. Results: Overall, 770 patients (NALIRIFOX, n = 383; Gem+NabP, n = 387) were included. Baseline characteristics were balanced between arms. At a median follow-up of 16.1 months, 544 events had occurred. Median OS was 11.1 months in the NALIRIFOX group versus 9.2 months in the Gem+NabP group; median PFS was 7.4 months versus 5.6 months. Median (95% CI) duration of response was 7.3 (5.8–7.6) and 5.0 (3.8–5.6) months in patients who received NALIRIFOX and Gem+NabP, respectively. Grade 3/4 treatment-emergent adverse events occurring in at least 10% of patients receiving NALIRIFOX versus Gem+NabP included diarrhea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), hypokalemia (15.1% vs 4.0%), anemia (10.5% vs 17.4%) and neutropenia (14.1% vs 24.5%). Conclusions: First-line NALIRIFOX demonstrated clinically meaningful and statistically significant improvement in OS and PFS compared with Gem+NabP in patients with mPDAC. The NALIRIFOX safety profile was consistent with the profiles of the regimen components and generally manageable. Clinical trial information: NCT04083235. Research Sponsor: Ipsen.

<table>
<thead>
<tr>
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<th>NALIRIFOX (n = 383)</th>
<th>Gem+NabP (n = 387)</th>
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<tbody>
<tr>
<td>OS, months, median (95% CI)</td>
<td>11.1 (10.0–12.1)</td>
<td>9.2 (8.3–10.6)</td>
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<td>HR (95% CI); p value</td>
<td>0.83 (0.70–0.99); 0.04</td>
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<tr>
<td>OS rate, %</td>
<td>45.6</td>
<td>39.5</td>
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<td>OS, months, median (95% CI)</td>
<td>26.2 (24.8–27.5)</td>
<td>19.3</td>
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<td>PFS, months, median (95% CI)</td>
<td>7.4 (6.0–7.7)</td>
<td>5.6 (5.3–5.8)</td>
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<tr>
<td>HR (95% CI); p value</td>
<td>0.69 (0.58–0.83); &lt; 0.0001</td>
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<tr>
<td>PFS rate, %</td>
<td>27.4</td>
<td>13.9</td>
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<tr>
<td>ORR, % (95% CI)</td>
<td>41.8 (36.8–46.9)</td>
<td>36.2 (31.4–41.2)</td>
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Tucatinib and trastuzumab for previously treated HER2-positive metastatic biliary tract cancer (SGNTUC-019): A phase 2 basket study.

Yoshiaki Nakamura, Nobumasa Mizuno, Yu Sunakawa, Erika P. Hamilton, Hidetoshi Hayashi, Seung Tae Kim, Keun-Wook Lee, Bradley J. Monk, Danny Nguyen, Alicia Frances Clare Okines, David M. O’Malley, Paula R Pohlmann, Martin Reck, Evan Y. Yu, Roman Groisberg, Jorge Ramos, Qianwen Tan, Tom Stinchcombe, Tanios S. Bekaii-Saab; National Cancer Center Hospital Japan East, Kashiwa, Japan; Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan; St. Marianna University School of Medicine, Kawasaki, Japan; Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; Kindai University Faculty of Medicine, Osaka-Sayama, Japan; Samsung Medical Center, Seoul, South Korea; Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; Division of Gynecological Oncology, HonorHealth Research Institute, University of Arizona College of Medicine, Phoenix and Creighton University School of Medicine, Phoenix, AZ; City of Hope-Natrona Long Beach, Long Beach, CA; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Division of Gynecologic Oncology, Ohio State University, James Comprehensive Cancer Center, Columbus, OH; University of Texas MD Anderson Cancer Center, Houston, TX; Lungen Clinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research (DZL), Grosshansdorf, Germany; Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA; Merck, & Co Inc., Rahway, NJ; Seagen, Inc., Bothell, WA; Duke Cancer Institute, Duke University School of Medicine, Durham, NC; Mayo Clinic, Scottsdale, AZ

Background: Biliary tract cancer (BTC) is an aggressive malignancy with a poor prognosis, and current treatment options for advanced BTC are limited, with second-line therapy, FOLFOX and S-1 offering an objective response rate (ORR) of 5.0% and 7.5%, respectively. Up to 20% of BTCs overexpress human epidermal growth factor receptor 2 (HER2). Tucatinib (TUC) is a highly selective HER2-directed TKI approved for HER2-positive (HER2+) metastatic breast and colorectal cancer. Discussed here are the efficacy and safety results of TUC combined with Trastuzumab (Tras) in pts with previously treated HER2+ metastatic BTC.

Methods: SGNTUC-019 (NCT04579380) is an open-label phase 2 basket study evaluating efficacy, safety, and tolerability of TUC and Tras in pts with HER2-altered solid tumors. Pts in the BTC cohort had been previously treated with and progressed after $\geq 1$ line of systemic therapy for metastatic disease. Eligible pts had locally determined HER2+ (defined as HER2 overexpression determined by immunohistochemistry [IHC] 3+ or HER2 amplification determined by in situ hybridization assay or next-generation sequencing) metastatic BTC. Pts were treated on a 21-day cycle with TUC (300 mg orally twice a day) and Tras (8 mg/kg IV followed by 6 mg/kg every 3 wks). Disease status was determined based on RECIST v1.1 with assessments performed every 6 wks for 24 wks and every 12 wks thereafter. The primary endpoint is confirmed objective response rate (cORR) per investigator assessment. Secondary endpoints include overall survival (OS), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and safety.

Results: Thirty pts were enrolled in the BTC cohort as of data cutoff date of 30 Nov 2022. The median duration of follow-up was 8.3 months. cORR was 46.7% (90% CI, 30.8, 63.0), with 14 responses including 1 complete and 13 partial responses. Median DOR was 6.0 months (90% CI, 5.5, not estimable). DCR was 76.7% (n=23; 90% CI, 60.6, 88.5), and median PFS was 5.5 months (90% CI, 3.9, 8.1). At data cutoff, 13 (43.3%) patients had died, and the 12-months OS rate was 53.8% (90% CI, 35.2, 69.1%). Overall, the most common treatment-emergent adverse events (TEAEs) reported were pyrexia (43.3%) and diarrhea (40.0%). Grade $\geq 3$ TEAEs were reported in 18 (60.0%) of 30 pts; however, only 6 (20.0%) and 2 (6.7%) of these pts had Grade $\geq 3$ TEAEs related to TUC and Tras, respectively. Two (6.7%) pts discontinued TUC due to TEAEs, cholangitis and liver disorder. No deaths were due to TEAEs.

Conclusions: The combination of TUC and Tras was well tolerated in pts with previously treated HER2+ metastatic BTC. The observed antitumor activity supports the combination of TUC and Tras as a future chemotherapy-free treatment option for this population with historically poor outcomes. Clinical trial information: NCT04579380. Research Sponsor: Seagen Inc.
Results from the pivotal phase (Ph) 2b HERIZON-BTC-01 study: Zanidatamab in previously-treated HER2-amplified biliary tract cancer (BTC).

Shubham Pant, Jia Fan, Do-Youn Oh, Hye Jin Choi, Jin Won Kim, Heung-Moon Chang, Lequn Bao, Hui-Chuan Sun, Teresa Macarulla Mercade, Feng Xie, Jean Philippe Metges, Ying Jeer, John A Bridgewater, Mohamedtaki Abdulaziz Tejani, Emerson Yu-sheng Chen, Harpreet Singh Wasan, Michel Pierre Druex, Jia-Fang Ma, Phillip M. Garfin, James J. Harding; MD Anderson Cancer Center, Houston, TX; Affiliated Zhongshan Hospital of Fudan University, Shanghai, China; Seoul National University Hospital, Seoul, Korea, Republic of (South); Severance Hospital Yonsei University Health System, Seoul, South Korea; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Asian Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; HuBei Cancer Hospital, HuBei, China; Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; The Third Affiliated Hospital of the Chinese PLA Naval Military Medical University, Shanghai, China; ICH CHRU de Brest - Hospital Morvan, ARPEGO Network, Brest, France; Zhejiang Cancer Hospital, Hangzhou, China; UCL Cancer Institute, London, United Kingdom; AdventHealth Cancer Institute, Orlando, FL; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; Imperial College Healthcare NHS Trust, London, United Kingdom; Paris Saclay University, Gustave Roussy, Villejuif, France; BeiGene Ltd., Beijing, China; Zymeworks BC Inc., Vancouver, BC, Canada; Memorial Sloan Kettering Cancer Center, New York, NY

Background: For patients (pts) with locally advanced/metastatic BTC who progress after first-line treatment (tx), standard tx offers limited clinical benefit with modest improvement in survival. HER2-targeted therapies have improved survival in breast and gastric cancer, but there is no approved HER2-targeted therapy for BTC. Zanidatamab (zani), a HER2-targeted bispecific antibody, has shown durable responses in a subset of pts with BTC in a Ph 1 trial. Methods: HERIZON-BTC-01, an open-label, global Ph 2b study (NCT04466891), evaluated zani (20 mg/kg IV every 2 wks) in pts with HER2-amplified, locally advanced unresectable or metastatic BTC (gallbladder cancer [GBC], intra-/extra-hepatic cholangiocarcinoma [ICC/ECC]) who had received prior gemcitabine-containing therapy; pts with prior HER2-targeted therapies were excluded. Pt cohort assignment was based on tumor immunohistochemistry (IHC) status: Cohort 1 for IHC 2+/3+ (HER2 positive), or Cohort 2 for IHC 0/1+. Tumors were assessed every 8 wks per RECIST 1.1. The primary endpoint was confirmed objective response rate (cORR) by independent central review (ICR) in Cohort 1. Secondary endpoints included other efficacy and safety outcomes. Results: Enrollment is complete with 87 pts (Cohort 1, n=80; Cohort 2, n=7) treated. Median age was 64 yrs (range, 32-79); 54% were female; 66% were Asian; 52% had GBC, 30% ICC, and 18% ECC. Pts had a median of 1 line (range, 1-7) of prior therapy in the locally advanced/metastatic setting. In Cohort 1, cORR was 41% with median duration of response (DOR) of 12.9 months (m; 95% CI: 5.95, not estimable); median study follow-up time was 12.4 m. Among the 33 responders at the data cut (10OCT2022), 49% had ongoing responses and 82% had a DOR of ≥16 wks. Median time to first response was 1.8 m (range, 1.6-5.5). Progression-free survival and overall survival are being evaluated. No responses were observed in Cohort 2. In both cohorts (N=87), tx-related adverse events (TRAEs) occurred in 72% of pts; TRAEs in ≥10% of pts were diarrhea (37%) and infusion-related reaction (33%). Gr 3 TRAEs occurred in 18% of pts, with diarrhea (4.6%) and ejection fraction (EF) decreased (3.4%) in >3% of pts. Two pts (2.3%) discontinued zani due to an AE (EF decreased and non-infectious pneumonitis). Seven pts had serious TRAEs; no AE preferred term occurred in >1 pt. No zani-related Gr 4 AEs or deaths were reported. Conclusions: Results of the pivotal HERIZON-BTC-01 study indicate that the HER2 bispecific antibody zani demonstrates rapid, durable responses with a manageable safety profile in pts with tx-refractory HER2-positive BTC. Given these data, zani continues to be developed as a tx option in HER2-positive BTC. Clinical trial information: NCT04466891. Research Sponsor: Zymeworks BC Inc.

<table>
<thead>
<tr>
<th>Cohort 1 (n=80)</th>
<th>Cohort 2 (n=7)</th>
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<tbody>
<tr>
<td>cORR, % (95% CI)</td>
<td>41 (30, 53)</td>
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<tr>
<td>Confirmed Best Objective Response, n (%)</td>
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<td>CR</td>
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<td>SD</td>
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<tr>
<td>PD</td>
<td>24 (30)</td>
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<td>Disease Control Rate, % (95% CI)</td>
<td>69 (57, 79)</td>
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Updated dose escalation results for ReFocus, a first-in-human study of highly selective FGFR2 inhibitor RLY-4008 in cholangiocarcinoma and other solid tumors.

Mitesh J. Borad, Alison M. Schram, Richard D. Kim, Suneel Deepak Kamath, Vaibhav Sahai, Efrat Dotan, Robin Kate Kelley, Mariano Ponz-Sarvise, Do-Youn Oh, Jeffrey Yachnin, Vaia Florou, Philippe Alexandre Cassier, Joon Oh Park, Chih-Yi Liao, Michael Millward, Florence (Tianhui) Ramirez, Fabien Jean Ricard, Antoine Hollebecque, Vivek Subbiah, Lipika Goyal; Mayo Clinic Arizona, Scottsdale, AZ; MSKCC, New York, NY; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Cleveland Clinic, Taussig Cancer Center, Cleveland, OH; University of Michigan, Ann Arbor, MI; Fox Chase Cancer Center, Philadelphia, PA; University of California, San Francisco, San Francisco, CA; Clinica Universidad de Navarra, Pamplona, Spain; Medical Oncology, Seoul National University Hospital, Seoul, Korea, Republic of (South); Karolinska University Hospital, Stockholm, Sweden; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Centre Léon Bérard, Lyon, France; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; University of Chicago Department of Medicine, Chicago, IL; Linear Clinical Research & University of Western Australia, Nedlands, Australia; Relay Therapeutics, Cambridge, MA; Gustave Roussy Cancer Institute, Villejuif, France; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital, Boston, MA

Background: Oncogenic FGFR2 alterations (fusions/rearrangements (f/r), amplifications, mutations) represent a broad therapeutic opportunity as they drive multiple solid tumors, particularly cholangiocarcinoma (CCA). However, off-isofrm toxicity and on-target resistance limit the benefit of approved pan-FGFR inhibitors (FGFRi). RLY-4008 is the first potent, highly selective, oral FGFR2 inhibitor designed to overcome these limitations by targeting FGFR2 driver alterations and resistance mutations. Here, we present updated dose escalation results from ReFocus (NCT04526106), a seamless Phase I/II, open label study evaluating the safety and preliminary efficacy of RLY-4008 in patients (pts) with advanced, FGFR2-altered solid tumors.

Methods: Adult pts received RLY-4008 BID, QD, discontinuous on a 4-week (wk) cycle following a Bayesian Optimal Interval design. Treatment-related adverse events (TRAEs), PK, ctDNA and anti-tumor activity (RECIST v1.1) were assessed.

Results: As of 30 Jan 23, 116 pts (82 f/r, 27 mutation, 6 amplification) received RLY-4008 at doses of 20-200 mg/day, including 91 with CCA. 50% had prior FGFRi, and median lines of prior therapies was 3 (1-15). 28/46 ct-DNA-evaluable pts with CCA with prior FGFRi had ≥1 baseline resistance mutation, most commonly at FGFR2 N549X (23/46) or V564X (17/46). RLY-4008 had favorable PK with doses ≥40 mg QD providing FGFR2 occupancy ≥90%. 70 mg QD was the RP2D based on PK, safety, anti-tumor activity and exposure-dependent tumor regressions in FGFRi-naïve CCA f/r pts. Anti-tumor activity was observed in CCA and solid tumors across doses and FGFR2 alterations with radiographic tumor reductions in 74 (64%), SD/PR in 83 (72%), including 4/4 (100%) FGFRi-naïve CCA f/r pts at RP2D achieving confirmed PR. Clinically meaningful disease control and durable responses were observed in pts with CCA. Overall, median treatment duration was 24 wks (range 1-108 wks). 105 pts discontinued (PD (81%), AE (3%), other (7%)). Across doses, most common TRAEs were low-grade PPE (57%), stomatitis (56%), dry mouth (38%), alopecia (28%), and dry eye (22%). No grade 4/5 TRAEs were observed.

Conclusions: These encouraging dose escalation data confirm the broad therapeutic potential of highly selective FGFR2 targeting with RLY-4008 by demonstrating encouraging initial efficacy across FGFR2-altered solid tumors and genomic alterations, with a differentiated safety profile that avoids FGFR1- and FGFR4-related toxicity. Phase 2 of ReFocus continues across solid tumors and with registrational intent in FGFRi-naïve, FGFR2 f/r CCA. Clinical trial information: NCT04526106. Research Sponsor: Relay Therapeutics.
Results from the MORPHEUS-liver study: Phase Ib/II randomized evaluation of tiragolumab (tira) in combination with atezolizumab (atezo) and bevacizumab (bev) in patients with unresectable, locally advanced or metastatic hepatocellular carcinoma (uHCC).

Richard S. Finn, Baek-Yeol Ryoo, Chih-Hung Hsu, Daneng Li, Adam Burgoyne, Christopher Cotter, Shreya Badhinarayanan, Yulei Wang, Anqi Yin, Tirupathi Rao Edubilli, Edward Gane; University of California Los Angeles, Los Angeles, CA; Asan Medical Center, Seoul, South Korea; National Taiwan University Hospital, Taipei, Taiwan; City of Hope Comprehensive Cancer Center, Los Angeles, CA; UC San Diego, San Diego, CA; Genentech, Inc., South San Francisco, CA; Roche (China) Holding Ltd., Shanghai, China; Roche Products Ltd., Welwyn Garden City, United Kingdom; University of Auckland, Auckland, New Zealand

Background: Atezo + bev is the current first-line standard of care for uHCC based on the IMbrave150 study, which demonstrated superior overall survival, progression-free survival (PFS), and objective response rate (ORR) vs sorafenib (Finn, et al. New Engl J Med 2020; Cheng, et al. J Hepatol 2022). TIGIT is a novel inhibitory immune checkpoint present on activated T cells and NK cells. Tira (anti-TIGIT) may synergize with other immunotherapies, such as PD-L1/PD-1 inhibitors. The MORPHEUS platform comprises multiple phase Ib/II trials to identify early efficacy signals and safety of treatment combinations across cancers. Here we report data from a cohort of the MORPHEUS-liver study (NCT04524871) evaluating the combination of tira + atezo + bev vs a control arm (atezo + bev) in patients with uHCC. Methods: Patients with previously untreated uHCC were randomized to receive atezo (1200mg IV) + bev (15mg/kg IV) with or without tira (600mg IV) every three weeks. The primary endpoint was investigator-assessed ORR by RECIST V1.1. Secondary endpoints included PFS and safety. Results: A total of 58 patients were randomized (tira + atezo + bev, n=40; atezo + bev, n=18). As of 28 November 2022, median follow up was 14.0 months in the tira + atezo + bev arm and 11.8 months in the control arm. Confirmed ORR was higher in the tira + atezo + bev arm (42.5%) vs the control arm (11.1%). Median PFS was longer with tira + atezo + bev (11.1 months; 95% CI: 8.2–NE) vs control (4.2 months; 95% CI: 1.6–7.4), corresponding to a PFS hazard ratio (HR) of 0.42 (95% CI: 0.22–0.82). A similar pattern of increased ORR and PFS was observed for the treatment arms in both PD-L1+ (n=23) and PD-L1– (n=27) subgroups. For tira + atezo + bev vs control arm, grade 3/4 treatment-related AEs were 27.5% vs 33.3% and AEs leading to any treatment discontinuation were 22.5% vs 22.2%, respectively. Conclusions: The addition of tira to atezo + bev resulted in higher ORR and longer PFS compared with atezo + bev, and no new safety signals were identified. These data suggest that tira + atezo + bev may be a promising novel first-line treatment option for patients with uHCC, and support further study in this setting. Clinical trial information: NCT04524871. Research Sponsor: F. Hoffmann-La Roche Ltd.

<table>
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<th>Efficacy outcomes</th>
<th>Tira + atezo + bev</th>
<th>Atezo + bev</th>
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<tr>
<td>ITT, n</td>
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<td>18</td>
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<tr>
<td>Confirmed ORR, % (n/N)</td>
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<td>11.1 (2/18)</td>
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<td>(95% CI)</td>
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<td>(1.4–34.7)</td>
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<td>Median PFS, months (95% CI)</td>
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<td>HR (95% CI)</td>
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<td>PD-L1+, n</td>
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<td>7</td>
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<tr>
<td>Confirmed ORR, % (n/N)</td>
<td>56.3 (9/16)</td>
<td>14.3 (1/7)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>13.6 (7.1–NE)</td>
<td>2.8 (2.3–NE)</td>
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<td>Median PFS, months (95% CI)</td>
<td>9.1 (4.0–NE)</td>
<td>4.2 (1.5–7.4)</td>
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<td>HR (95% CI)</td>
<td>0.36 (0.14–0.94)</td>
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Subgroup analysis of double-blind, placebo-controlled Ph. 2 study of nanvuranlat in treatment of pre-treated, advanced, refractory biliary tract cancer (BTC): Patients with high LAT1 expression and response to nanvuranlat.

Masafumi Ikeda, Makoto Ueno, Masayuki Furukawa, Chigusa Morizane, Tetsuo Takehara, Tomohiro Nishina, Akiko Todaka, Naohiro Okano, Kazuo Hara, Yousuke Nakai, Kazuyoshi Ohkawa, Takashi Sasaki, Kazuya Sugimori, Naoyuki Yokoyama, Kouji Yamamoto, Junji Furuse; Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Kanagawa Cancer Center, Yokohama, Japan; National Kyushu Cancer Center, Fukuoka, Japan; National Cancer Center Hospital, Tokyo, Japan; Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Japan; Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; Kyorin University, Mitaka, Japan; Aichi Cancer Center, Aichi Hospital, Nagoya, Japan; Department of Urology, Faculty of Medicine, The University of Tokyo, Bunkyo-Ku, Japan; Osaka International Cancer Institute, Osaka-Shi, Japan; The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Koto-Ku, Japan; Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; Niigata City General Hospital, Niigata City, Japan; Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan

**Background:** L-type amino acid transporter 1 (LAT1, SLC7A5) is overexpressed in cancer cells leading to aggressive proliferation and lymphatic metastases. LAT1 sustains energy resources by supplying essential amino acids to the TCA cycle in chemotherapy-resistant cancer cells. LAT1 is a documented marker of poor prognosis. In a placebo-controlled, randomized trial involving patients with pre-treated, advanced, refractory biliary tract cancer (BTC), monotherapy with nanvuranlat (JPH203), a selective LAT1 inhibitor, demonstrated a significant improvement in progression free survival (PFS) compared to placebo. Subgroup analysis was conducted to determine whether the level of expression of LAT1 affects nanvuranlat efficacy. **Methods:** Patients with four different subtypes of advanced BTC were enrolled: intrahepatic and extrahepatic cholangiocarcinoma, and gallbladder and ampulla of Vater cancers. All were refractory to or intolerant of standard chemotherapy and other investigational medicines. Our analysis compared efficacy and safety in the subgroup with high LAT1 expression and all patients group. LAT1 expression was immunohistochemically evaluated in tumor specimens of BTC patients at baseline, as defined by Yanagisawa N, et al. (Cancer Med 2014). **Results:** At data cut-off (Feb 28, 2022), 211 BTC patients consented at 14 centers in Japan, and 104 patients were randomized (2:1) to nanvuranlat (n = 69) or placebo (n = 35) as the full analysis set (FAS) population. Among the samples immunohistochemically evaluable for LAT1, 62.5% had high LAT1 expression. There was no significant difference in background demography between all patient group and the high-LAT1 subgroup. Nanvuranlat met its primary endpoint (FAS by the blinded independent central review (BICR)), demonstrating a statistically significant improvement in PFS by BICR in comparison with the placebo group. The hazard ratios were further improved with nanvuranlat versus placebo, on analysis of the high-LAT1 subgroup of patients in both PFS and OS. Safety was comparable between nanvuranlat and placebo, on analysis of the high-LAT1 subgroup. **Conclusions:** This subgroup analysis indicates that the efficacy of nanvuranlat in PFS and OS is enhanced in BTC patients with high LAT1 expression, when compared with placebo. Safety profiles were similar for nanvuranlat- and placebo-treated patients in this subgroup analysis. Clinical trial information: UMIN000034080. Research Sponsor: J-Pharma Co., Ltd.
KEYNOTE-859 study of pembrolizumab plus chemotherapy for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: Outcomes in the protocol-specified PD-L1–selected populations.

Sun Young Rha, Lucjan Wynicz, Patricio Eduardo Yanez Weber, Yuxian Bai, Min-Hee Ryu, Jeeyun Lee, Fernando Rivera, Gustavo Vasconcelos Alves, Marcelo Garrido, Kai-Keen Shiu, Manuel González Fernández, Jin Li, Mavee Aine Lowery, Timucin Cil, Felipe Melo Cruz, Shukui Qin, Lina Yin, Sonal Bordia, Pooja Bhagia, Do-Youn Oh; Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea, Republic of (South); Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Universidad de La Frontera, James Lind Cancer Research Center, Temuco, Chile; Harbin Medical University Cancer Hospital, Harbin, China; Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South); Samsung Medical Center, Seoul, South Korea; University Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain; Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; Pontificia Universidad Católica de Chile, Santiago, Chile; University College Hospital, NHS Foundation Trust, London, United Kingdom; IMAT-Oncomedica, Monteria, Colombia; Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; Trinity St. James Cancer Institute, Dublin, Ireland; Health and Science University, Adana City Hospital, Adana, Turkey; Núcleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; Cancer Center of People’s Liberation Army, Nanjing, China; Merck & Co., Inc., Rahway, NJ; Seoul National University College of Medicine, Seoul, Korea, Republic of (South)

Background: In the ITT population of the KEYNOTE-859 study of HER2-negative, advanced G/GEJ cancer (NCT03675737), pembrolizumab (pembro) + chemotherapy (chemo) significantly improved OS (HR 0.78, 95% CI 0.70-0.87; \( P < 0.0001 \)), PFS (HR 0.76, 95% CI 0.67-0.85; \( P < 0.0001 \)), and ORR (51.3% vs 42.0%; \( P = 0.00009 \)) vs placebo + chemo at the protocol-specified interim analysis. The safety profile of pembro + chemo was as expected. We present efficacy outcomes of the protocol-specified PD-L1 combined positive score (CPS) \( \geq 1 \) and CPS \( \geq 10 \) populations. Methods: Eligible pts aged \( \geq 18 \) y with HER2-negative, previously untreated locally advanced or metastatic G/GEJ adenocarcinoma, ECOG PS 0-1, and known PD-L1 CPS were randomized 1:1 to pembro 200 mg or placebo IV Q3W for \( \leq 35 \) cycles, both given with investigator’s choice of 5-FU + cisplatin (FP) or capecitabine + oxaliplatin (CAPOX). Randomization was stratified by region (Europe/Israel/North America/Australia vs Asia vs rest of world), PD-L1 CPS \( < 1 \) vs \( \geq 1 \), and chemo (FP vs CAPOX). Per protocol, the primary endpoint of OS and the secondary endpoints of PFS and ORR per RECIST v1.1 by blinded independent central review were tested in the PD-L1 CPS \( \geq 1 \) and \( \geq 10 \) populations. Data are from the interim analysis (median study follow-up, 31.0 mo). Results: At baseline, 618 (78.2%) of 790 pts randomized to pembro + chemo and 617 (78.2%) of 789 pts randomized to placebo + chemo had PD-L1 CPS \( \geq 1 \); 279 (35.3%) and 272 (34.5%), respectively, had CPS \( \geq 10 \). Baseline characteristics were generally consistent between treatment arms and populations. In the PD-L1 CPS \( \geq 1 \) population, median OS was 13.0 mo (95% CI 11.6-14.2) for pembro + chemo vs 11.4 mo (95% CI 10.5-12.0) for placebo + chemo (HR 0.74, 95% CI 0.65-0.84; \( P < 0.0001 \)), median PFS was 6.9 mo (95% CI 6.0-7.2) vs 5.6 mo (95% CI 5.4-5.7) (HR 0.72, 95% CI 0.63-0.82; \( P < 0.0001 \)), ORR was 52.1% vs 42.6% (\( P = 0.00001 \)), and median DOR was 8.3 mo (range 1.2+ to 41.5+) vs 5.6 mo (1.3+ to 34.2+). In the PD-L1 CPS \( \geq 10 \) population, median OS was 15.7 mo (95% CI 13.8-19.3) with pembro + chemo vs 11.8 mo (95% CI 10.3-12.7) with placebo + chemo (HR 0.65, 95% CI 0.53-0.79; \( P < 0.0001 \)), median PFS was 8.1 mo (95% CI 6.8-8.5) vs 5.6 mo (95% CI 5.4-6.7) (HR 0.62, 95% CI 0.51-0.76; \( P < 0.0001 \)), ORR was 60.6% vs 43.0% (\( P = 0.00001 \)), and median DOR was 10.9 mo (range 1.2+ to 41.5+) vs 5.8 mo (1.4+ to 31.2+). Among all treated pts in the pembro + chemo (n = 785) and placebo + chemo (n = 787) arms, immune-mediated AE incidence was 27.1% vs 9.3%. Conclusions: The addition of pembro to FP or CAPOX significantly improved OS, PFS, and ORR in the PD-L1 CPS \( \geq 1 \) and \( \geq 10 \) populations. Together with the efficacy and safety results from the ITT population, these data support pembro + chemo as a new first-line treatment option for pts with locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma, regardless of PD-L1 expression. Clinical trial information: NCT03675737. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
A phase 2 randomized, open-label, multicentre study of sintilimab and anlotinib in combination with gemcitabine plus cisplatin (GemCis) as first-line therapy in patients (pts) with advanced biliary tract cancer (BTC): SAGC.

Li Jingjing, Qi Xu, Xiaoqing Xu, Luo Cong, Jieer Ying; Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hangzhou, China; Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hangzhou, China; Zhejiang Cancer Hospital, Hangzhou, China

Background: BTC has a higher incidence in China rather than worldwide, with extremely poor prognosis, and the efficacy of standard first-line therapy is rather limited. TOPAZ-1 study suggested the immune check-point inhibitor plus chemotherapy as first line in advanced BTC significantly improved OS and PFS with manageable safety, but the median OS was just 12.8 months. SAGC is the first randomized controlled phase 2 trial to evaluate immune check-point inhibitor plus antiangiogenic targeted drug plus chemotherapy in advanced BTC as first-line treatment.

Methods: Overall 80 advanced BTC were randomized 1:1 to receive sintilimab (200mg every 3 weeks [Q3W]) and anlotinib (10mg po qd, Days 1-14 Q3W) in combination with GemCis (Gem 1000 mg/m2 and Cis 25 mg/m2 on Days 1 and 8 Q3W) for up to 8 cycles, followed by sintilimab (200mg every 3 weeks [Q3W]) and anlotinib (10mg po qd, Days 1-14 Q3W) (SAGC group) or GemCis (Gem 1000 mg/m2 and Cis 25 mg/m2 on Days 1 and 8 Q3W) for up to 8 cycles until disease progression or unacceptable toxicity (GC group). The primary objective was to assess the progression-free survival (PFS). Secondary endpoints included, objective response rate (ORR), overall survival (OS) and safety. Next generation sequencing (NGS) was performed on pre-treatment available tumor tissue in 58 patients to screen dominant patients of the therapy.

Results: At the time of the final data cutoff (Sep. 22,2022), median follow-up was 13.4 mo, and 65/80 pts (81.3%) had discontinued tx. The confirmed median PFS was 8.6 months for SAGC group vs. 6.2 months for GC group (HR 0.79, p < 0.01) and ORR was 52.8% for SAGC group vs. 29.4% for GC group. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 77.5% of pts receiving sintilimab plus anlotinib plus GemCis and 40% of pts receiving GemCis. The results from NGS suggested that patients with TMB-H and ARID1A-WT may benefit more from combination therapy.

Conclusions: In pts with advanced BTC, sintilimab plus anlotinib plus GemCis significantly improved PFS and ORR vs GemCis with manageable safety, indicating sintilimab plus anlotinib plus GemCis may be a new first-line standard of care regimen. Clinical trial information: NCT04300959. Research Sponsor: None.
A randomized study of consolidation chemoradiation (CTRT) vs observation after first-line chemotherapy (CT) in advanced gall bladder cancers (GBC): RACE-GB Study.

Sushma Agrawal, Rahul Rahul, Ashish Singh, Prabhakar Mishra, Rajan Saxena; SGPGI, Lucknow, India; Sanjay Gandhi Postgraduate institute of Medical Sciences, Lucknow, India; Sanjay gandhi Postgraduate Institute of medical sciences, Lucknow, India

Background: CT (gemcitabine plus cisplatin) is the standard of care for patients presenting with unresectable advanced GBC but their prognosis remains poor. The value of CTRT after CT is uncertain. We therefore conducted a randomised trial evaluating consolidation CTRT versus Observation after four cycles of CT in those patients whose disease did not progress during CT (NCT05493956). Methods: Responders (partial response and stable disease) to 4 cycles of CT were randomised to CTRT vs observation (n=135). CTRT was delivered by 3D-Conformal Radiation Therapy along-with concurrent capecitabine @1250 mg/m2. The dose of RT was 45 Gy in 25 fractions to GBC and lymphatics followed by a boost of 9 Gy in 5 fractions to the GBC. The primary endpoint was overall survival which was calculated from the date of randomisation. The trial is designed to detect an improvement in 2-year OS from 8% in the control arm to 25% in study arm with 80.0% power at a 0.05 significance level. The required sample size was 130 (65 in each arm) over a duration of 4-5 years. CTRT was delivered by 3DCRT along-with concurrent capecitabine @1250 mg/m2. The dose of RT was 45Gy in 25 fractions to GBC and lymphatics followed by a boost of 9 Gy in 5 fractions to the GBC. Toxicities documented during CT and CTRT were recorded using the CTCAE version 3.0. and RTOG criteria respectively. Chi square test and Survival analysis was performed for the data analysis. Demographic data and CTRT Dose volume data were correlated with side effects and survival. Statistical analysis was performed with SPSS version-23. Results: 67 patients were randomized to observation and 68 to CTRT. Their demographic characteristics were well balanced. 63% were women, 58% had T4 tumours, 42% had N2, 27% needed stenting for obstructive jaundice. The median overall survival in the CTRT arm was 10 months versus 4 months in the observation arm (HR 0.47 [95% CI 0.33-0.68] p=0.001). Adverse events (grade 3 or higher) due to CTRT included the following: Nausea 3%, Anemia 9%, GI bleed 6%, hepatotoxicity 13%. Updated survival data and prognostic factors affecting overall survival will be presented in the meeting. Conclusions: CTRT after 4 cycles of CT significantly prolonged overall survival but was also associated with adverse events. Clinical trial information: NCT05493956. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.
A multicenter, open-label, randomized phase II study evaluating adjuvant gemcitabine plus cisplatin (GC) and capecitabine with concurrent capecitabine radiotherapy (CAPE-RT) in patients with operated gallbladder adenocarcinoma (GBC): The GECCOR-GB trial.

Anant Ramaswamy, Vikas S. Ostwal, Reena Engineer, Manali Parulekar, Sarika Mandavkar, Nanda Aier, Prabhat Ghanshyam Bhargava, Sujay Srinivas, Shraddha Patkar, RAHUL KRISHNATRY, Shivakumar Gudi, Akhil Kapoor, Durgatosh Pandey, Swapnil Patel, Abhishek Shinghal, Alok Goel, Tapas Kumar Dora, Debasish Chaudhary, Suman Kumar Ankathi, Mahesh Goel; Tata Memorial Hospital (HBNI), Mumbai, India; HBNI University, Mumbai, India; Homi Bhabha Cancer Hospital, Varanasi, Varanasi, India; Homi Bhabha Cancer Hospital, Sangrur, Sangrur, India; Homi Bhabha Cancer Hospital &Research Centre, Sangrur, India; Homi Bhabha Cancer Hospital, Sangrur, India; Tata Memorial Center (HBNI), Mumbai, India

Background: Adjuvant gemcitabine plus cisplatin (GC) and concurrent chemo-radiotherapy are commonly used treatment options for resected GBC. Methods: GB-GECCOR is a multicentre, open-label randomized non-comparative phase II study in patients of Gallbladder cancer (GBC), with R0 or R1 resection within 3 months of randomization. Patients were randomized 1:1 to GC arm (Gem 1000 mg/m2 and Cisplatin 25mg/m2 on day 1 and 8, q 3 weeks) for 6 cycles or CAPE-RT arm (Capecitabine 1000mg/m2 BD on days 1-14, q 3 weeks for 2-4 cycles followed by chemoradiation (RT: 45 Gy over 25 fractions concurrent with capecitabine: 825mg/m2 twice) followed by 2-4 cycles of capecitabine for a total of 6 cycles). The primary end point was 1-year disease-free survival (DFS). With 80% power to detect the difference between a 59% (minimum sufficient activity of the regimen) and a 77% (sufficient activity for future larger studies with the regimen) 1-year DFS rate assuming an attrition of 10%, a total of 90 patients were required for the study. Results: Between May 2019 and February 2022, 90 patients (45 in each arm), were included. Stage II and stage III GBC were seen in 50 (56%) and 40 patients (44%) respectively, with R0 resection observed in 86 patients (96%). Patient characteristics were well balanced between the 2 arms except for R1 resections which were greater in the CAPE-RT arm (p=0.041). With a median follow-up duration of 23 months, the 1-year DFS rate was 88.9% (95% CI: 79.5-98.3) in the GC group and 77.8% (95% CI: 65.4 – 90.2) in the CAPE-RT group, respectively. The most common AEs were grade 3/4 neutropenia in 6 patients (13.3%) in the GC group and grade 2/3 HFS in 14 patients (31.1.%) in the CAPE-RT group. The distant metastases were seen in 12 patients (26.6 %) in each arm and loco-regional metastases in 3 patients (6.6 %) in the GC arm. Conclusions: In this study of operated GBC, GC and CAPE-RT successfully achieved the minimum pre-specified DFS rates. Within the confines of a non-comparative randomised study, GC had narrowed the gap in survivals of stage III vs. stage II GBCs, which was not noted in the CAPE-RT arm. This study results give credence to the use of both regimens as reasonable standards of care till evaluation in larger phase 3 studies. Clinical trial information: CTRI/2019/05/019323. Research Sponsor: Educational grants to the institute from reddy’s lab Pvt for this study.

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<th>Characteristics</th>
<th>GC arm (%)(n=45)</th>
<th>CAPE-RT arm (%) (n=45)</th>
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<td>1-year DFS</td>
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<td>77.8% (95% CI: 65.4 – 90.2)</td>
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<tr>
<td>Stage II</td>
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<tr>
<td>Stage III</td>
<td>81.4</td>
<td>73.1% (59.9-86.3)</td>
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<td>2-year DFS</td>
<td>74.8% (95% CI: 60.4-89.2)</td>
<td>73.1% (59.9-86.3)</td>
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<tr>
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<tr>
<td>1-year OS</td>
<td>95.6% (95% CI: 89.4 – 98.7)</td>
<td>88.9 (95% CI: 79.5-98.3)</td>
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Clinical and genomic characterization of early-onset pancreatic cancer.

Florian Castet, Carles Fabregat Franco, Gloria Castillo, Victor Navarro, Eduardo García-Galea, Alexandre Sierra, Ana Carmona-Alonso, Tian Tian, Ana Vivancos, Teresa Macarulla; Gastrointestinal and Endocrine Tumor Unit, Vall d’Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d’Hebron, Vall d’Hebron Barcelona Hospital Campus, Barcelona, Spain; Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; Oncology Data Science (ODysSey) Group, Vall d’Hebron Institute of Oncology (VHIO), Vall d’Hebron Barcelona Hospital Campus, Barcelona, Spain; Preclinical and Translational Research Program, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Barcelona, Spain; Cancer Genomics Group, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Pancreatic cancer is a leading cause of cancer-related death worldwide. Early-onset tumours (≤ 50 years) have risen alarmingly in recent years. However, the clinical and genomic particularities of early-onset pancreatic cancer (EOPC) remain poorly defined. We aimed to characterize EOPC and study its implications for treatment and prognosis.

Methods: We performed a retrospective analysis of EOPC patients and a control group of patients ≥ 70 years (defined as average-onset pancreatic cancer, AOPC) followed at a tertiary cancer centre from 2010 to 2022. We collected baseline patient characteristics, tumor molecular profiling, germline genetic alterations, survival and treatment outcomes. We used a targeted gene panel to identify somatic genomic events and classified them according to the ESMO scale for clinical actionability of molecular targets (ESCAT). Key molecular findings were validated in an external cohort. We used a propensity score weighting method and multivariate Cox regression analysis to adjust for covariates.

Results: We reviewed 824 patients, 336 of whom met all inclusion criteria (EOPC N = 139, AOPC N = 197). EOPC was associated with smoking status (current, 15.9 vs 7.9%, p = 0.03), lower prevalence of diabetes (3.7 vs 39.6%, p < 0.01), better performance status (ECOG 0, 42.9 vs 19.3%, p < 0.01), higher CA19.9 levels (median 574 vs 207.6UI/L, p = 0.07) and higher albumin levels (median 4.2 vs 3.9g/L, p < 0.01). EOPC showed a non-significant higher prevalence of germline alterations (22.4 vs 14.5%, p = 0.18). After adjustment for baseline covariates, we observed no differences in survival (HR 0.94, 95% CI 0.63-1.4). We found a lower prevalence of KRASWT tumors in EOPC when compared with AOPC (83.1 vs 91.1%, p = 0.12) and validated this finding in an independent cohort of 803 patients (82.9 vs 94.5%, p < 0.01). Notably, EOPC were enriched in potentially actionable alterations when compared with AOPC, both in our cohort (19.1 vs 14.4%) and the validation cohort (14.4 vs 7.9%, p < 0.01). Moreover, 294 patients in our cohort (EOPC N = 130; AOPC N = 164) were diagnosed with or eventually presented metastasis. EOPC more frequently received first-line 5FU-based chemotherapy (44.1 vs 14.7%, p < 0.01) and received a greater number of treatment lines (median 2 vs 1, p < 0.01). EOPC had a longer progression-free survival on first-line chemotherapy when compared with AOPC (HR 0.61, 95% CI 0.43-0.87, p < 0.01) although there were no differences in response rate. Six EOPC patients received matched targeted therapies and 5 patients with AOPC. After adjusting for the number of treatment lines received, EOPC treated with targeted therapies exhibited longer OS compared with EOPC who did not (HR 0.34 95% CI 0.12-0.93, p = 0.04), whereas this trend was not observed in AOPC (HR 0.82 95% CI 0.32-2.11, p = 0.68).

Conclusions: EOPC patients harbor unique clinical and molecular features and may particularly benefit from precision-based oncology approaches. Research Sponsor: None.
Investigating alterations in cancer driver genes and other potentially targetable mutations in patients with intrahepatic cholangiocarcinoma (iCCA) treated on the randomised phase III multicentre BILCAP clinical trial.

Valerie Elizabeth Crolley, Rachel Guest, Andrew David Beggs, Eleanor Jaynes, Steve Thorn, Javier Herrero, Ian Tomlinson, Juan W. Valle, John Neil Primrose, John A Bridgewater; UCL-University College London (United Kingdom), London, United Kingdom; University of Edinburgh, Edinburgh, United Kingdom; Institute of Cancer & Genomic Sciences, University of Birmingham, Birmingham, United Kingdom; University of Southampton NHS Foundation Trust, Southampton, United Kingdom; Bill Lyons Informatics Centre, London, United Kingdom; University of Oxford, Oxford, United Kingdom; Division of Cancer Sciences, The University of Manchester/The Christie NHS Foundation Trust, Manchester, United Kingdom; University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; UCL Cancer Institute, London, United Kingdom

**Background:** The BILCAP clinical trial established adjuvant capecitabine as the standard of care treatment in patients with resected biliary tract cancer. Translational work to investigate the role of cancer driver genes and other potentially targetable mutations in patients enrolled on BILCAP was performed, with this analysis focusing on patients with intrahepatic cholangiocarcinoma (iCCA).

**Methods:** Archived fixed formalin (FFPE) tissue samples were collected from consented BILCAP patients. These samples underwent DNA and RNA extraction followed by low-pass whole genome sequencing (lp-WGS), targeted gene sequencing (TGS) and RNA sequencing (RNAseq) for copy number (CN) analysis, mutation analysis and gene fusion analysis.

**Results:** 84 of the 447 BILCAP patients had iCCA; 45 successfully underwent lp-WGS and RNAseq, of whom 36 also underwent TGS. The median age was 61 years (95% CI 57.8 – 64.2), 55.6% were female and 23 received capecitabine (51.1%). FGFR2 gene fusions were present in 9 patients (20.0%), as were fusions in NTRK1 (n = 3, 6.7%), FGFR1 (n = 3, 6.7%), FGFR3 (n = 2, 4.4%) and FGFR4 (n = 2, 4.4%). Commonly mutated driver genes included ROS1 (n = 12, 33.3%), MET (n = 10, 27.8%) and ALK (n = 7, 19.4%) with known pathogenic variants seen in IDH1 (n = 4, 11.1%; total number of mutations = 7, 19.4%), B RAF (n = 2, 5.6%; total n = 6, 16.7%), FGFR2 (n = 1, 2.7%; total n = 8, 22.2%), FGFR3 (n = 1, 2.7%, total n = 6, 16.7%), IDH2 (n = 1, 2.7%; total n = 6, 16.7%) and EGFR (n = 1, 2.7%; total n = 4, 11.1%). Commonly amplified (CN ≥ 4, ploidy < 3) genes included NTRK1 (n = 9, 20.0%), ERBB2 (n = 8, 17.8%), and MET (n = 3, 6.7%). Most of the alterations investigated in this cohort did not significantly affect recurrence risk or overall survival (OS), including FGFR2 fusions (OS HR 1.23, p = 0.695; recurrence HR 1.32 p = 0.555). However, the presence of a FGFR3 fusion gene significantly reduced OS (OS HR 6.57, p = 0.0091; recurrence HR 3.71, p = 0.0734), and having ≥ 4 copies of either NTRK1 (OS HR 3.55, p = 0.0027; recurrence HR 3.48, p = 0.0019) or MET (OS HR 6.06, p < 0.001; recurrence HR 6.05 p < 0.001) significantly reduced OS and increased the risk of recurrence.

**Conclusions:** The BILCAP cohort shows a wide variety of driver and potentially targetable mutations in unselected iCCA patients, comparable to previous early-stage biliary tract cancer datasets. Of note, patients with FGFR3 fusions, MET amplification or NTRK1 amplification had significantly shorter OS, and patients with MET or NTRK1 amplification had significantly reduced OS and significantly increased risk of disease recurrence. MET amplification, NTRK1 amplification and FGFR3 fusions may be important indicators in determining prognosis, and could provide attractive targets for future targeted anti-cancer therapy in iCCA. Clinical trial information: EUCTR2005-003318-13. Research Sponsor: Incyte.
Not all treated KRAS-mutant pancreatic adenocarcinomas are equal: KRAS G12D and survival outcome.

Bach Ardalan, Aaron Ciner, Yasmine Baca, Sourat Darabi, Anup Kasi, Emil Lou, Jose Ignacio Azqueta, Joanne Xiu, Chadi Nabhan, Anthony F. Shields, Andrew Aguirre, Harshabad Singh, Rachna T. Shroff, Michael J. Pishvaian, Sanjay Goel; Sylvester Comprehensive Cancer Center, Miami, FL; University of Maryand, Baltimore, MD; Caris Life Sciences, Phoenix, AZ; Hoag Memor Hosp, Newport Beach, CA; University of Kansas Cancer Center, Westwood, KS; University of Minnesota, Minneapolis, MN; University of Miami Sylvester Cancer Center, Miami, FL; Barbara Ann Karmanos Cancer Institute, Detroit, MI; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Brookline, MA; University of Arizona Cancer Center, Tucson, AZ; Johns Hopkins University School of Medicine, Washington, DC; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: KRAS is an oncogenic driver in pancreatic ductal adenocarcinoma (PDAC) with mutations identified in > 90% of cases. G12D is the most frequent variant, followed by G12V and G12R. We recently reported on the prognostic impact of distinct KRAS mutations. The current study utilized a large clinical and genomic database, to further explore and characterize the prognostic and molecular differences between KRAS variants, focusing on KRAS G12D and G12R. Methods: PDAC samples were tested using whole transcriptome sequencing (WTS; Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) at Caris Life Sciences (Phoenix, AZ). Transcriptomic signatures including MPAS (MAPK activation score), T-cell inflamed score and tumor microenvironment (TME) characterization were calculated on WTS data. Significance was determined by X² and Fisher-Exact and p-value was adjusted for multiple comparisons (q). Real-world overall survival (rWOS) obtained from insurance claims data was calculated from tissue collection to last contact (comparison done by Kaplan–Meier test). Results: 5,555 PDAC patients harboring either KRAS G12D (n = 2,671), G12V (n = 1,871) G12R (n = 904) or G12C (n = 109) variants were identified. Patients with KRAS G12R mutant tumors had significantly longer OS compared to G12D (396 vs 311 days, HR 0.81, CI 0.74-0.88, p = 0.0001). There was no difference among KRAS variants in the rate of TP53, CDKN2A and SMAD4 mutations. ARID1A and KMT2D were more frequently mutated in KRAS G12D vs. G12R. The MPAS gene signature reflecting MAPK pathway activation trended lower in G12R vs. G12D. Expression of multiple genes in this pathway was statistically lower in the G12R cohort. Immune profiling suggested that: PDL1 expression is significantly lower in G12R vs G12D (13% vs 19%), TMB-H and dMMR were comparable in G12D vs G12R and several glucose and glutamine metabolism genes were significantly lower in expression when comparing G12R vs G12D - table. OS was improved within the G12R cohort for those patients on metformin (n = 273 patients) (416 vs 388 days, HR 0.84, CI 0.72-0.99, p = 0.037) while no difference was seen in those with KRAS G12D based on metformin use. Conclusions: Patients with G12D mutations have significantly lower survival compared to G12R. Significant molecular differences were seen in MAPK pathway gene expression, markers of immune activation, and genes involved in glucose and glutamine metabolism. Intriguingly, metformin use appeared to impact survival in the KRAS G12R subgroup. We aim to further explore distinct vulnerabilities based on MAPK pathway activation and dysregulated metabolism. Based on this data, future studies should address the KRAS mutation status and explore distinct therapeutic vulnerabilities. Research Sponsor: None.

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<th>Association</th>
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FOOTPATH: A randomized, open-label phase-2 study of liposomal irinotecan + 5-FU and folinic acid (NAPOLI) versus sequential NAPOLI and mFOLFOX6 versus gemcitabine/nab-paclitaxel in treatment-naive metastatic pancreatic cancer (mPDAC).

Benedikt Westphalen, Tobias Gaska, Maximilian Reichert, Michael Quante, Helmut Oettle, Dirk Thomas Waldschmidt, Anke Schlenska-Lange, Stefan Angermeier, Ludwig Fischer von Weikersthal, Wolfram Bohle, Ursula Vehling-Kaiser, Arndt Stahler, Stephan Kanizer, Christof Lamberti, Uwe Pelzer, Marianne Sinn, Wolfgang Blau, Stefan Hubert Boeck, Swantje Held, Volker Heinemann; Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany; Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Leopoldina Krankenhaus, Medizinische Klinik 2, Schweinfurt, Germany; Klinikum Coburg, Coburg, Germany; Department of Hematology, Oncology and Tumorimmunology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Universitätsklinikum Hamburg-Eppendorf II, Medizinische Klinik, Hamburg, Germany; HELIOS Dr. Horst Schmidt Klinik, Wiesbaden, Germany; Universitätsklinikum der LMU, Medizinische Klinik und Poliklinik III and Comprehensive Cancer Center Munich, München, Germany; Clinassess Inc., Leverkusen, Germany; Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany

Background: The optimal first-line regimen in the treatment of mPDAC remains unknown. Recent data demonstrated superiority of 5-FU/liposomal irinotecan/oxaliplatin (NALIRIFOX) over gemcitabine/nab-paclitaxel. However, the question remains open if both irinotecan and oxaliplatin are required in first-line treatment and whether these agents can be given sequentially. Methods: Eligible patients with histologically confirmed diagnosis of mPDAC were randomized 1:1:1 to receive in Arm A standard treatment (gemcitabine 1000 mg/m² + nab-paclitaxel 125 mg/m²) or investigational therapy applying in Arm B the NAPOLI regimen (liposomal irinotecan 80 mg/m² + folinic acid 400 mg/m² + 5-FU 2400 mg/m²) or in Arm C a sequence of NAPOLI and mFOLFOX6 (oxaliplatin 85mg/m² + folinic acid 400mg/m² + 5-FU 2400 mg/m²). Overall, 274 patients were enrolled at 48 sites in Germany. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), objective response rate, disease control rate, duration of study treatment and safety. Results: In the full analysis set (n=265), neither treatment with NAPOLI (3.1 months, HR 1.224, p=0.2123) nor the sequence of NAPOLI and mFOLFOX6 (6.0 months, HR 0.864 p= 0.0720) lead to a statistically significant improvement of PFS over gemcitabine/nab-paclitaxel (4.3 months). Median duration of treatment was 3.5 months in Arm A, 2.0 months in Arm B and 3.7 months in Arm C, respectively. In a first analysis of overall survival, OS in Arm A was 8.7 months (95% CI, 7.1-11.9 months) versus 7.9 months in Arm B (95% CI, 6.6-12.3 months; HR 1.178, P= 0.348) and 11.0 months in Arm C (95% CI, 8.4-13.6 months; HR 0.879, P=0.154). Overall, safety was comparable with published data, with higher rates of neutropenia and peripheral neuropathy in Arm A, while diarrhea was more frequent in Arms B and C. Conclusions: The study did not show superiority of either NAPOLI or the sequence of NAPOLI/mFOLFOX6 over standard therapy with gemcitabine/nab-paclitaxel. In view of the published evidence, the present data supports the hypothesis that sequential NAPOLI/mFOLFOX6 may be equally effective with regard to OS, but less toxic, compared to mFOLFIRINOX. Clinical trial information: NCT03487016. Research Sponsor: Servier.
Prospective evaluation of the utility of concurrent 18F-FDG PET/CT and 68Ga-DOTA-TOC imaging in gastroenteropancreatic neuroendocrine neoplasms (GEPNENs): The PETNET study.

Joao Paulo Solar Vasconcelos, Marilyn Zhou, Pavithraa Ravi, Hayley Allan, Heather Saprunoff, Ingrid Bloise, Sara Harsini, Don Wilson, Francois Benard, Patrick Martineau, Jonathan M. Loree; BC Cancer, Vancouver Cancer Centre, Vancouver, BC, Canada; BC Cancer, Vancouver, BC, Canada; BC Cancer Research Institute, Vancouver, BC, Canada; BCCA, Vancouver Cancer Centre, Vancouver, BC, Canada

Background: Somatostatin receptor imaging (SRI) is a standard of care for patients with GEPNENs. The additional value of concurrent 18F-FDG PET/CT (FDG PET) remains unclear. We reviewed a prospective functional imaging study to determine the utility of FDG PET in GEPNENs. Methods: PETNET is a prospective study in British Columbia, Canada, which provides all 68Ga-DOTA-TOC (DOTA PET) imaging in the province. Every patient receives a DOTA PET scan and an FDG PET within 30 days. PETNET enrolls all patients with an indication for SRI. Scans are ordered per treating physician discretion at any point in the disease course. This abstract focuses on the WD-GEPNEN population. Only the first dual functional imaging scans were analyzed and FDG was interpreted qualitatively (positive/negative). Results: From 04/2017-01/2023, 375 patients with NEN were enrolled, 165 (44%) with metastatic GEPNENs. Baseline characteristics are described. Median time between scans was 4 days (IQR 1-11). The proportion of patients with positive FDG PET at baseline increased with WHO grade. For patients with well differentiated G1 to G3 GEPNENs (N=161), overall survival was significantly lower with a positive FDG PET (HR: 4.22; 95%CI 1.61-11.02 p=0.001). FDG remained prognostic when G3 tumors were excluded (N=148) (HR 3.52; 95%CI 1.32-9.42 p=0.007). When analyzing dual tracer PET imaging, patients with DOTA+/FDG- had reduced risk of dying in comparison with DOTA+/FDG+ (HR:0.26; 95%CI 0.09-0.67 p=0.01). After multivariate analysis, FDG positivity remained independently associated with reduced survival (HR 2.87; 95%CI 1.06-7.75 p=0.04) when controlling for grade of tumor and age. Conclusions: In this prospective cohort of metastatic GEPNENs, a positive FDG PET was significantly associated with reduced overall survival. These results provide additional evidence to support dual tracer functional imaging use in metastatic well differentiated GEPNEN’s. Research Sponsor: BC Cancer foundation.

Baseline characteristics.

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<th>Number of Patients (%)</th>
<th>G1</th>
<th>G2</th>
<th>G3 Well Dir</th>
<th>G3 Poor Dir</th>
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<td>165 (100)</td>
<td>73 (44.2)</td>
<td>75 (45.7)</td>
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<th>Median Time from Diagnosis to scan, Days (IQR)</th>
<th>665 (120-1863)</th>
<th>491 (120-2165)</th>
<th>814 (137-1822)</th>
<th>67 (27-665)</th>
<th>1086 (1065-1107)</th>
<th>1334 (752-1916)</th>
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<th>Primary site</th>
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<th>Pancreas (%)</th>
<th>Other (%)</th>
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<td>47 (64.4)</td>
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Neoadjuvant hepatic arterial infusion chemotherapy with FOLFOX could improve outcomes of resectable BCLC stage A/B hepatocellular carcinoma patients beyond Milan criteria: A multi-center, phase 3, randomized, controlled clinical trial.

Wei Wei, Shaohua Li, Rongce Zhao, Yuan Cheng, Qiang Li, Lianghe Lu, Jie Mei, Changzhen Shang, Rui Luo, Mingxin Pan, Bangle Xiang, Yuchuan Jiang, Qiucheng Lei, Mingrong Cao, Ji-Bin Li, Lie Zheng, Huanwei Chen, Jian-Hong Zhong, Chong Zhong, Rongping Guo; Sun Yat-sen University Cancer Center, Guangzhou, China; Zhujiang Hospital, Guangzhou, China; The First Affiliated Hospital, Jinan University, Guangzhou, China; Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China; Department of Hepatobiliary Surgery, the First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, P. R. China., Guangzhou, China; Zhujiang Hospital of Southern Medical University, Guangzhou, China; Guangxi Medical University Cancer Hospital, Nanning, China; Department of General Surgery, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, P. R. China., Guangzhou, China; The First People’s Hospital of Foshan, Foshan, Guangdong, P. R. China., Foshan, China; Clinical Trials Center, Sun Yat-sen University Cancer Center, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Department of Imaging, Sun Yat-sen University Cancer Center, Guangzhou, China; Foshan First People’s Hospital, Foshan, Guangdong, China; The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Arlington, MA

Background: The efficacy of operation, as the only radical option for resectable BCLC stage A/B hepatocellular carcinoma (HCC) patients beyond Milan criteria, is still unsatisfactory. This study aimed to investigate to efficacy and safety of preoperative neoadjuvant hepatic arterial infusion chemotherapy (HAIC) with FOLFOX regimen for these patients. Methods: In this multi-center, prospective, phase 3, randomized, open-labeled, controlled clinical trial, resectable BCLC stage A/B HCC patients beyond Milan criteria were randomly assigned (1:1) before hepatectomy to receive either neoadjuvant HAIC (treatment group) or operation directly without any neoadjuvant treatment (control group). The primary endpoint was overall survival (OS), the secondary endpoints are progression-free survival (PFS) and safety. Results: Between March 2016 and August 2022, a total of 487 patients were screened from seven Chinese hospitals, and 392 patients were randomly assigned to receive neoadjuvant FOLFOX-HAIC before hepatectomy (treatment group, n = 195), or operation directly without any neoadjuvant treatment (control group, n = 197) and were included in the ITT population. Among them, 14 patients from the treatment group and 13 patients from the control group were excluded from the PP population. In the ITT population, the OS rates at 1-, 2-, and 3-year were 97.7%, 86.3%, and 77.1%, respectively, for the treatment group and were 90.0%, 80.9%, and 70.6%, respectively, for the control group. The median PFS of the treatment and control groups was 17.4 months (95% CI, 9.0-25.8) and 9.8 months (8.2-11.4), respectively, in the ITT population. The OS and PFS were significantly better in treatment group than in control group (p = 0.032 and < 0.001, respectively) in ITT population. In the PP population, the OS rates at 1-, 2-, and 3-year were 98.7%, 91.1%, and 79.7%, respectively, for the treatment group and were 89.2%, 79.3%, and 67.7%, respectively, for the control group. The median PFS of the treatment and control groups was 22.7 months (95% CI, 10.9-34.5) and 10.2 months (8.4-12.1), respectively, in the PP population. The OS and PFS were significantly better in treatment group than in control group (p = 0.001 and < 0.001, respectively) in PP population. In treatment group of ITT population, the complete regression (CR) rate, objective response rate (ORR), disease control rate (DCR) was 11.3%, 61.5%, and 97.4%, respectively. Safety analysis showed HAIC was quite safe, 191 (97.9%) patients had mild HAIC related adverse events (HRAEs) (grade 0-2). The operation related adverse events (ORAEs) were similar between two groups (p = 0.265). Conclusions: Neoadjuvant HAIC with FOLFOX regimen before hepatectomy may bring survival benefits for resectable BCLC stage A/B HCC patients beyond Milan criteria. Clinical trial information: NCT03851913. Research Sponsor: None.
Preliminary translational immune and stromal correlates in a randomized phase II trial of pembrolizumab with or without defactinib for resectable pancreatic ductal adenocarcinoma (PDAC).

Anser Ali Abbas, John Davelaar, Jessica Gai, Zachariah Brown, Abrahm Levi, Sheila Linden, Angela Minasyan, Christina Rodriguez, Jonathan A. Pachter, Jun Gong, Brent K Larson, Andrew Eugene Hendifai, Simon Lo, Srivivas Gaddam, Kambiz Kosari, Nicholas Nissen, Stephen Jacob Pandol, Richard Burkhart, Lei Zheng, Arsen Osipov; Cedars-Sinai Medical Center, Los Angeles, CA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Verastem, Inc., Needham, MA; Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA

Background: PDAC is an aggressive cancer and refractory to immunotherapy due to its immunosuppressive tumor microenvironment (TME). Focal adhesion kinase (FAK) is a master regulator of the TME and associated with TME immune suppression. Our current randomized phase II trial evaluates the use of pembrolizumab, a programmed cell death 1 (PD-1) immune checkpoint inhibitor, with or without defactinib, a FAK inhibitor (FAKi), as sequential neoadjuvant and adjuvant therapy in patients with high risk resectable PDAC. We hypothesize that the patients receiving pembrolizumab and defactinib treatment will exhibit a decrease in immunosuppressive fibroblasts and myeloid subtype populations, leading to increased CD8+ T-cell infiltration into the TME compared to patients receiving pembrolizumab alone.

Methods: We performed quantitative analysis of multiplex immunohistochemistry (miHC) using 40 biomarkers, evaluating immune and stromal cell types on 14 pre-treatment biopsies and post-treatment resections of PDAC patients enrolled in our platform neoadjuvant clinical trial (NCT03727880). All patients received 2 cycles of gemcitabine+nab-paclitaxel neoadjuvant chemotherapy and underwent a biopsy after completion of chemotherapy. Patients randomized to Arm A received 2 cycles of pembrolizumab 200 mg IV every 3 weeks and defactinib 400 mg PO BID, and those randomized to Arm B received pembrolizumab alone, followed by surgical resection. Image cytometry was used to quantify immune cell populations and colocalize biomarker expression in distinct cell types. Cell populations were compared using unpaired T-tests. Results: Lower FAP+ fibroblast density was significantly associated with higher CD8+ T-Cell infiltration in Arm A (p=0.002), but not in Arm B. Patients in Arm A demonstrated a 5.44-fold average increase in CD8+ T-cell percentage between pre-immunotherapy treatment and post-immunotherapy treatment specimens compared to a 2.01-fold increase in patients in Arm B (p=0.02, p=0.09, respectively). Only patients in Arm A showed a significant increase in M1 macrophage cell density (p=0.02) after treatment. Both arms increased in CXCR4+ cell percentage (p=0.011, p=0.06) following neoadjuvant immunotherapy; however, the increase in Arm A was less than in Arm B (0.72 and 0.84-fold, respectively). Conclusions: In this analysis, pembrolizumab combined with defactinib was associated with lower fibroblast infiltration, higher anti-tumor M1 macrophage expression and increased CD8+ T-cell infiltration into the TME, versus pembrolizumab alone. The increased expression of CXCR4 across both treatment arms may represent a resistance mechanism and supports CXCR4 as an additional TME target. These preliminary findings warrant continued research into FAK inhibition and immune checkpoint combinatorial strategies. Clinical trial information: NCT03727880. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.
Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649.

Yelena Y. Janjigian, Kohei Shitara, Markus H. Moehler, Marcelo Garrido, Carlos Gallardo, Lin Shen, Kensei Yamaguchi, Lucjan Wyrwicz, Tomasz Skoczylas, Arinilda Silva Campos Bragagnoli, Tianshu Liu, Mustapha Tehfe, Elena Elimova, Ricardo Elias Bruges Maya, James M. Cleary, Michalis Karamouzis, Samira Soleymani, Ming Lei, Carlos Amaya-Chanaga, Jaffer A. Ajani; Memorial Sloan Kettering Cancer Center, New York, NY; National Cancer Center Hospital East, Kashiwa, Japan; Johannes-Gutenberg University Clinic, Mainz, Germany; Clinica San Carlos de Apoquindo, Pontificia Universidad Católica, Santiago, Chile; Fundacion Arturo López Pérez, Providencia, Chile; Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; The Cancer Institute Hospital of JFCR, Tokyo, Japan; Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; II Klinika Chirurgii Ogólnej, Gastroenterologicznej i Nowotworów Ukurow Pokarowego, Medical University of Lublin, Lublin, Poland; Fundacao Pio XI Hosp Cancer De Barretos, Barretos, Brazil; Zhongshan Hospital, Fudan University, Shanghai, China; Oncology Center—Centre Hospitalier de l’Universite de Montreal, Montreal, QC, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Instituto Nacional de Cancerologia E.S.E., Bogotá, Colombia; Dana-Farber Cancer Institute, Boston, MA; Laiko General Hospital of Athens, Athens, Greece; Bristol Myers Squibb, Princeton, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: NIVO + chemo demonstrated superior overall survival (OS) and clinically meaningful progression-free survival (PFS) benefit vs chemo and acceptable safety in previously untreated patients (pts) with advanced GC/GEJC/EAC, leading to approvals in multiple countries including the US. NIVO + chemo continued to demonstrate clinically meaningful improvement in efficacy after 2 years of follow-up. We present efficacy and safety analyses from NIVO + chemo vs chemo from the 3-year follow-up of CheckMate 649. Methods: Adults with previously untreated, unresectable advanced, or metastatic GC/GEJC/EAC were enrolled, regardless of programmed death ligand 1 (PD-L1) expression, excluding pts with known HER2-positive status. Pts were randomized to NIVO (360 mg Q3W or 240 mg Q2W) + chemo (XELOX Q3W or FOLFOX Q2W), NIVO + ipilimumab, or chemo. Primary endpoints for NIVO + chemo vs chemo were OS and PFS by blinded independent central review (BICR) in pts with PD-L1 combined positive score (CPS) ≥ 5. Results: 1581 pts were concurrently randomized to NIVO + chemo or chemo. With 36-month (mo) minimum follow-up, NIVO + chemo continued to demonstrate OS and PFS benefit vs chemo in pts with PD-L1 CPS ≥ 5 and all randomized pts. The objective response rate (ORR) per BICR in pts with PD-L1 CPS ≥ 5 who had measurable lesions at baseline was 60% (95% CI 55–65) with NIVO + chemo vs 45% (95% CI 40–50) with chemo; in all randomized pts, ORR per BICR was 58% (95% CI 54–62) with NIVO + chemo vs 46% (95% CI 42–50) with chemo. Responses were more durable with NIVO + chemo vs chemo in pts with PD-L1 CPS ≥ 5 (median [m] duration of response [mDOR] 9.6 mo [95% CI 8.2–12.4] vs 7.0 mo [95% CI 5.6–7.9], respectively) and in all randomized pts (mDOR 8.5 mo [95% CI 7.7–9.9] vs 6.9 mo [95% CI 5.8–7.2], respectively). OS benefit with NIVO + chemo was observed across most prespecified subgroups. No new safety signals were identified. A summary of treatment-related adverse events (TRAEs) is shown in the Table. Additional analyses will be presented. Conclusions: After 3 years of follow-up, NIVO + chemo continued to demonstrate clinically meaningful long-term survival benefit with acceptable safety, further supporting its use as a standard 1L treatment in previously untreated pts with advanced GC/GEJC/EAC. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.
Final survival results of ipilimumab or FOLFOX in combination with nivolumab and trastuzumab in previously untreated HER2 positive esophago gastric adenocarcinoma: The randomized AIO INTEGA trial.

Joseph Tintelnot, Alexander Stein, Lisa Paschold, Elay Goekkurt, Christoph Schultheiß, Peter C. Thuss-Patience, Sylvie Lorenzen, Thomas Jens Ettrich, Jorge Riera Knorrenschold, Lutz Jacobsbach, Stefan Kubicka, Salah-Eddin Al-Batran, Anke C. Reinacher-Schick, Daniel Pink, Marianne Sinn, Udo Lindig, Axel Hinke, Susanna Hegewisch-Becker, Mascha Binder; University Cancer Center Hamburg (UCCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Hämatologisch-Onkologische Praxis Eppendorf (HOPE) and University Cancer Center Hamburg (UCCCH), Hamburg, Germany; Department of Internal Medicine IV, University Hospital Halle, Martin-Luther University Halle-Wittenberg, Halle, Germany; Hematology Oncology Practice Eppendorf and University Cancer Center Hamburg (UCCCH), Hamburg, Germany; Martin-Luther-Universität Halle-Wittenberg, Medizinische Fakultät, Halle, Germany; Charité–Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany; Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany; Ulm University, Ulm, Germany; Uniklinik Marburg, Marburg, Germany; Onkologische Schwerpunktpraxis, Dresden, Germany; Cancer Center Reutlingen, Reutlingen, Germany; Krankenhaus Nordwest, University Cancer Center Frankfurt and Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany; St. Josef Hospital, Ruhr-Universität Bochum, Bochum, Germany; Helios Klinikum Bad Saarow, Bad Saarow, Germany; Universitätsklinikum Hamburg-Eppendorf II. Medizinische Klinik, Hamburg, Germany; Universitätsklinikum Jena, Klinik für Innere Medizin II, Jena, Germany; CCRC, Duesseldorf, Germany; Hämatologisch-Onkologische Praxis Eppendorf (HOPE), Hamburg, Germany; Department of Internal Medicine IV, University Medical Center Halle (Saale), Halle, Germany

Background: In metastatic esophagogastric adenocarcinoma (EGA), the addition of PD-1 inhibitors (i) to chemotherapy has improved the outcome in selected patient populations. The randomized INTEGA trial investigated trastuzumab and PD-1i with FOLFOX or CTLA-4i in 1st line treatment of advanced HER2+ EGA. Methods: Patients with previously untreated, metastatic HER2+ (local IHC3+ or 2+/ISH+) EGA, and adequate organ function were randomized to trastuzumab and nivolumab (1mg/kg Q3W x4 /240mg Q2W for up to 12 months) in combination with ipilimumab (3mg/kg x4 Q3W; Ipi arm) or mFOLFOX6 (FOLFOX arm) accompanied by a large translational program. The primary endpoint was the 12month overall survival (OS) rate. The trial was registered at ClinicalTrials.gov, NCT03409848. Results: Between March 2018 and May 2020, 97 patients were enrolled and 88 randomized across 21 German sites with the following baseline characteristics: female/male 18/70, median age 60.5 (range 41-80), ECOG 0/1 54/34, GEJ/stomach 66/22. Central post hoc biomarker analysis on 82 evaluable patients showed PD-L1 CPS>1 in 59/46 patients and confirmed HER2 (central IHC3+ or 2+/ISH+) positivity in 77 patients. The observed OS rate at 12 months was 70% (95% confidence interval (CI) 54-81%) in the FOLFOX arm, and 57% (95% CI 41-71%) in the Ipi arm. The progression free survival was 10.7 and 3.2 months, and the overall response rate was 53.5% and 34% in the FOLFOX and the Ipi arm, respectively. Although these data are in favor of the FOLFOX arm, the overall survival curves crossed with increased follow-up (median follow-up of 18.8 months) and thus the final median OS was 22.1 and 23.3 months, numerically favoring the Ipi arm. According to the centrally assessed CPS the OS was: 22.1 and 32.2 months in the CPS<5 group, and 22.7 and 12.6 months in the CPS>5 group for the FOLFOX and the Ipi arm, respectively. Notably, the median tumor burden calculated as the sum of target lesions was numerically lowest in the Ipi arm with higher than median OS. Conclusions: In contrast to limited short term efficacy of the Ipi arm as reflected by the lower PFS, the Ipi arm showed favorable OS, that was inversely correlated to the CPS status. Further analysis of baseline clinical and molecular data to better identify the subgroup of patients benefitting the most of trastuzumab/nivolumab/ipilimumab will be presented at the meeting. Clinical trial information: NCT03409848. Research Sponsor: BMS.
A phase 2 study (DisTinGuish) of DKN-01 in combination with tislelizumab + chemotherapy as first-line (1L) therapy in patients with advanced gastric or GEJ adenocarcinoma (GEA).

Samuel J Klempner, Bassam Bassam Sonbol, Zev A. Wainberg, Hope Elizabeth Uronis, Vi Kien Chiu, Aaron James Scott, Syma Iqbal, Mohamedtaki Abdulaziz Tejani, Melissa C Stilian, Mathis Thoma, Michael Kagey, Jason Baum, Cynthia A. Sirard, Rachel A Altura, Jaffer A. Ajani; Mass General Cancer Center, Boston, MA; Mayo Clinic, Phoenix, AZ; University of California, Los Angeles, Medical Center, Los Angeles, CA; Duke University Medical Center, Durham, NC; The Angeles Clinic & Research Institute, Los Angeles, CA; University of Arizona Cancer Center, Tucson, AZ; University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA; AdventHealth Cancer Institute, Orlando, FL; Leap Therapeutics, Cambridge, MA; Leap Therapeutics, Inc., Cambridge, MA; MD Anderson Cancer Center, Houston, TX

Background: DKN-01 is an anti-DKK1 mAb which has demonstrated anti-tumor activity in patients with advanced GEA with low tumor PD-L1 expression, a subset with very limited therapeutic options. DKN-01 has immunomodulatory activity, stimulates a pro-inflammatory tumor microenvironment, and upregulates PD-L1 levels. Here we present 2-year survival data for 1L advanced GEA patients who received combination treatment with DKN-01, the Fc-optimized anti-PD-1 tislelizumab, and CAPOX chemotherapy. The ORR was previously reported (68% in ITT and 79% in PD-L1-low populations).

Methods: This Phase 2, multi-center, single arm Part A of the DisTinGuish (NCT04363801) study investigated DKN-01 + tislelizumab + CAPOX as 1L therapy in advanced HER2(-) GEA, regardless of DKK1 and PD-L1 expression levels. Tumor DKK1 and PD-L1 were assessed by central laboratories. The primary endpoint was ORR in a modified intent to treat population (>1 dose DKN-01); secondary endpoints included PFS and OS in the ITT population.

Results: Twenty-five patients were enrolled from September 2020 to April 2021. As of 23 January 2023: Median age was 61 years (22, 80); 17 patients had GEJ adenocarcinoma; 8 had gastric cancer. Twenty-one patients had tumors with evaluable DKK1 expression. Twenty-two patients had tumors with evaluable PD-L1 expression; the majority (73%) were low expressors (vCPS <5%). Median (m) duration on treatment is 11.3 months (mo). Seven patients remain on study, with 4 on-treatment beyond 2 years. The mPFS is 11.3 mo in the overall ITT population and 10.7 mo in patients with low tumor PD-L1 expression. The mOS is 19.5 mo in the overall ITT population and 18.7 mo in the patients with low tumor PD-L1 expression. Treatment related adverse events (TRAEs) were mild with most G1/2. The most common AEs related to the study drug regimen were nausea (72%), diarrhea (64%) and fatigue (60%). Five patients experienced G3 DKN-01-TRAEs including decreased neutrophil count (1), diarrhea (1), vomiting (1), hypophosphatemia (2), and pulmonary embolism (1). Conclusions: At 2-years of follow-up, 1L treatment of advanced GEA patients with DKN-01 in combination with tislelizumab and CAPOX resulted in a prolongation of PFS and OS compared with the modern SOC regimen of nivolumab plus chemotherapy, both in the overall population (mPFS 11.3 vs 7.7 mo; mOS 19.5 vs 13.8 mo) and in the PD-L1 low subgroup (mPFS 10.7 vs 7.5 mo; mOS 18.7 vs 12.4 mo), alongside a manageable safety profile. The prolonged PFS and OS observed in the current study are notable, especially in our trial population dominated by patients with tumors of low PD-L1 expression, where the known benefit of anti-PD-1 therapy is limited. The ongoing Part C of this study is evaluating mFOLFOX6/CAPOX plus tislelizumab with or without DKN-01 in the same 1L GEA patient population. Further evaluation of biomarkers is also ongoing. Clinical trial information: NCT04363801. Research Sponsor: Leap Therapeutics.
AdvanTIG-105: A phase 1b dose-expansion study of ociperlimab (OCI) + tislelizumab (TIS) with chemotherapy (chemo) in patients (pts) with stage IV gastric/gastroesophageal adenocarcinoma (GC/GEJC).

Se Hyun Kim, Gyeong-Won Lee, Byoung Yong Shim, David R. Spigel, Her-Shyong Shiah, Sophia Frentzas, Harry H. Yoon, Feng Wang, Meili Sun, Timothy Dudley Clay, Hao Zheng, Wei Tan, Ziqi Zhou, Ruihua Wang, Yi Ba; Seoul National University Bundang Hospital, Seongnam, South Korea; Division of Hematology-Oncology, Department of Internal Medicine, Institute of Health Science, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Jinju, Korea, Republic of (South); The Catholic University of Korea, St. Vincent’s Hospital, Suwon, Korea, Republic of (South); Department of Thoracic Medical Oncology, Sarah Cannon Research Institute/ Tennessee Oncology, Nashville, TN; Taipei Tzu Chi Hospital, Taipei City, Taiwan; Department of Medical Oncology, Monash Health and Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia; Mayo Clinic, Rochester, MN; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Jinan Central Hospital, Jinan, China; St. John of God Subiaco Hospital, Perth, Western Australia, Australia; BeiGene (USA) Co., Ltd., San Mateo, CA; BeiGene (Shanghai) Co., Ltd., Shanghai, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) inhibitor in combination with an anti-programmed cell death protein 1 (PD-1) antibody has shown antitumor activity in solid tumors. AdvanTIG-105 (NCT04047862) is a phase I/1b open-label study designed to assess the safety and preliminary antitumor activity of OCI, an anti-TIGIT monoclonal antibody (mAb), + TIS, an anti-PD-1 mAb, in pts with unresectable, locally advanced or metastatic solid tumors. In the dose-escalation part, OCI + TIS was well tolerated with preliminary antitumor activity observed, and the recommended phase 2 dose (RP2D) of OCI 900 mg intravenously (IV) every three weeks (Q3W) + TIS 200 mg IV Q3W was established. We report results from the dose-expansion part (GC/GEJC Cohort 9) of the AdvanTIG-105 study. Methods: Eligible pts had histologically/cytologically confirmed stage IV GC/GEJC. Pts were excluded if they had squamous cell, undifferentiated or other histological types of GC, had GC/GEJC with positive HER2 expression, or if they had received any prior therapy for metastatic disease. Pts received either the RP2D of OCI + TIS with oxaliplatin + capecitabine Q3W for 6 cycles (C), followed by maintenance therapy with the RP2D of OCI + TIS, + capecitabine Q3W, or the RP2D of OCI + TIS with cisplatin + 5-fluorouracil Q3W for 6 C. Treatment continued until disease progression, intolerable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), duration of response (DoR), disease control rate (DCR) per RECIST v1.1, and safety. Results: As of September 29, 2022, 60 pts with a median age of 61.5 years (range 35-82) were enrolled; 59 were efficacy evaluable. Median study follow-up was 31.1 weeks (range 1.4-78.4). ORR was 50.8% (95% CI: 37.5, 64.1); DCR was 84.7% (95% CI: 73.0, 92.8) with a median DoR of 4.6 months (95% CI: 3.9, 7.1). Median PFS was 8.2 months (95% CI: 5.8, not evaluable). In a subgroup analysis, ORR in pts with PD-L1 tumor area positivity (TAP) score $\geq 5\%$ (n = 27) was 59.3% (95% CI: 38.8, 77.6), and 50.0% (95% CI: 30.7, 69.4) in pts with PD-L1 TAP < 5% (n = 28). All 60 pts reported $\geq 1$ treatment-emergent adverse event (TEAE), the most common being anemia (43.3%) and platelet count decreased (41.7%). In total, 43 pts (71.7%) had $\geq$grade 3 TEAEs and 28 (46.7%) had serious adverse events. TEAEs leading to discontinuation of TIS and OCI occurred in 5 (8.3%) pts. TEAEs led to death in 2 (3.3%) pts; one event (neutropenic sepsis) was related to chemo, while the other (pulmonary embolism) was not treatment related. Conclusions: OCI 900 mg + TIS 200 mg + chemo was generally well tolerated and showed encouraging antitumor activity in pts with stage IV GC/GEJC. Clinical trial information: NCT04047862. Research Sponsor: BeiGene, Ltd.; This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Emma Ashman, BSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.
A phase 2 study of HLX07 as monotherapy or combination therapy in patients with locally advanced, unresectable, or metastatic esophageal squamous cell carcinoma.

**Background:** Esophageal cancer is one of the most common cancers worldwide with esophageal squamous cell carcinoma (ESCC) being the predominant histological subtype. Most patients are diagnosed at the advanced stage, and the prognosis remains poor. About 40–84% of ESCC cases showed overexpression of EGFR which was related to shorter overall survival and disease-free survival, indicating that treatment targeting EGFR could be a new strategy. This study aimed to evaluate the efficacy and safety of HLX07, a novel recombinant humanized anti-EGFR monoclonal antibody (mAb), as monotherapy or combination therapy in patients with locally advanced, unresectable/metastatic ESCC.

**Methods:** In this open-label, multicenter phase 2 study, patients aged 18–75 years with histologically or cytologically confirmed locally advanced, unresectable/metastatic ESCC or esophageal adenosquamous carcinoma were enrolled. Patients with no prior systemic antitumor therapy were assigned to group A and given HLX07 1000 mg plus serplulimab 200 mg (anti-PD-1 mAb) and chemotherapy (5-FU 2400 mg/m² + cisplatin 50 mg/m²), Q2W IV. Patients who had failed first-line immuno-chemotherapy combination or at least two lines of other systemic antitumor therapy were assigned to group B and given HLX07 monotherapy (1000 mg Q2W IV). The primary endpoints were objective response rate (ORR) and progression-free survival (PFS) assessed by an independent radiological review committee and investigators per RECIST v1.1. Secondary endpoints included other efficacy measures, safety, pharmacokinetics, immunogenicity, and biomarker explorations.

**Results:** As of February 4, 2023, 49 patients were enrolled in group A (n=30) and group B (n=19), with a median age of 64.5 and 59.0 years, respectively. 26 (86.7%) patients in group A and all patients in group B were male. The median follow-up duration was 2.9 months, and the preliminary efficacy was presented. Among the 42 efficacy evaluable patients (29 in group A and 13 in group B), investigator-assessed ORRs were 55.2% (95% CI 35.7–73.6%) and 23.1% (95% CI 5.0–53.8%) in the respective groups. Investigator-assessed median PFSs were not reached in group A and 1.5 months (95% CI 1.2–not evaluable) in group B. 15 (50.0%) patients in group A and 5 (26.3%) in group B had grade ≥3 treatment-emergent adverse events (AEs). AEs of special interest were observed in 16 (53.3%) and 11 (57.9%) patients, respectively, most commonly rash (43.3% vs 47.4%) and hypomagnesemia (33.3% vs 36.8%). No drug-related death was reported.

**Conclusions:** The encouraging antitumor activity and manageable safety profile support further development of HLX07 as a new treatment option for patients with advanced ESCC, both in first-line and late-line settings. Clinical trial information: NCT05221658. Research Sponsor: Shanghai Henlius Biotech, Inc.
Expression molecular subtype as a predictor of outcomes of chemoradiotherapy for esophageal cancer.

Manabu Muto, Keiko Minashi, Tomonori Yano, Yusuke Amanuma, Ryu Ishihara, Akinori Watanabe, Chikatoshi Katada, Tomoki Yamatsui, Kayoko Matsuhashi, Hisashi Doyama, Takayuki Ando, Yasumasa Nishimura, Katsuyuki Sakanaka, Shigeru Tsuonoda, Shinya Ohashi, Juko Shimizu, Harue Tada, Ryujii Uozumi, Kengo Nagashima, Hiroki Sasaki; Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; Clinical Trial Promotion Department, Chiba Cancer Center, Chiba City, Chiba, Japan; Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan; Department of Clinical Trial Promotion, Chiba Cancer Center, Chiba, Japan; Osaka International Cancer Institute, Osaka, Japan; Kitasato University, Sagamihara, Japan; Kyoto University, Department of Therapeutic Oncology, Kyoto, Japan; National Cancer Center Hospital East, Kanazawa, Japan; Third Department of Internal Medicine, University of Toyama, Toyama, Japan; Kindai University Faculty of Medicine, Osaka-Sayama, Japan; Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan; Department of Surgery, Kyoto University, Kyoto, Japan; Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; Kyoto University, Kyoto, Japan; Translational Research Center, Kyoto University Hospital, Kyoto, Japan; Tokyo Institute of Technology, Meguro-Ku, Japan; Biostatistics Unit, Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan; Department of Translational Oncology, National Cancer Center Research Institute, Tokyo, Japan

Background: The standard treatment for advanced esophageal cancer is preoperative chemoradiotherapy (CRT) followed by surgery or definitive CRT (NCCN Guideline 2022 ver5). CRT has the advantage of preserving organs and functions and the prognosis for patients achieved complete response by CRT is good. However, it is currently impossible to predict the outcomes of CRT before treatment. We have performed RNA expression analysis of pre-treatment biopsy specimens of esophageal cancer and identified several intrinsic molecular subtypes, as well as E-type (high expression of squamous markers) with good prognosis for CRT and M2-type (high expression of stromal markers) with poor prognosis for CRT (US patent No 10,969,390 B2). Herein, we performed an integrated analysis to confirm the relationship between intrinsic expression molecular subtype classification and prognosis in the pooled population from two prospective cohort studies (UMIN000043637).

Methods: Two cohort studies were as follows; 1) single institute prospective cohort study conducted at National Cancer Center Hospital East (n=157, UMIN-C000000459), 2) multicenter prospective cohort study conducted at 10 institutions (n=226, UMIN000016141). A total 383 cases met inclusion criteria and the Affymetrix U331Plus 2 panel (47,104 transcripts, 38,572 genes) was used to identify E-type and M2-type. The clinical course and outcome were blinded for subtype classification. Treatment was performed as usual at each institution, and treatment details and outcomes were examined by subtype.

Results: Among 383 patients, 181 and 164 patients were treated by CRT and surgery, respectively. Ninety-nine percent (n=342) were squamous cell carcinoma. Stage I/II/III/IV were 13/61/86/21 and 17/63/81/3 in CRT group and surgery group, respectively. Among them, 76 (22%), 100 (29%), 169 (49%) patients were classified as E, M2 and others, respectively. Among the patients treated by CRT, CR rate of E-type and M2-type were 62.8% (95% CI, 47.8-75.7) and 33.3% (95% CI, 21.9-47.1) (p=0.006). The 5-year progression free survival (PFS) and overall survival (OS) rates of CRT group was 50.5% (95% CI, 34.7-64.4) and 59.8% (95% CI, 42.6-73.3) for E-type vs. 23.0% (95% CI, 12.0-36.2) and 29.0% (95% CI, 16.8-42.4) for M2-type, with statistically significant difference (p=0.011, p=0.003). Cox regression analysis showed that crude HR for PFS and OS of E vs M2 were 0.50 (95% CI, 0.296-0.859, p=0.012) and 0.41 (95% CI, 0.226-0.750, p=0.004), respectively. In contrast, E and M2-type did not show the survival difference in surgery group.

Conclusions: For the first time in the world, we confirmed that expression molecular subtype of esophageal cancer has the potential to predict the outcomes of CRT. The results may provide precision medicine in the selection of treatment for esophageal cancer. Research Sponsor: AMED Foundation in Japan.
A phase Ib/II, multicenter, open-label study of AK104, a PD-1/CTLA-4 bispecific antibody, combined with chemotherapy (chemo) as first-line therapy for advanced gastric (G) or gastroesophageal junction (GEJ) cancer: 2-Year update data.

Jiafu Ji, Lin Shen, Ziyu Li, Xiangyu Gao, Ke Ji, Ye Chen, Nong Xu, Tianshu Liu, Nong Yang, Haijun Zhong, Changzheng Li, Zengqing Guo, Qinxia Fan, Xiaoyan Lin, Zhifang Yao, Wei Liu, Zhongmin Maxwell Wang, Baiyong Li, Yu Xia; Peking University Cancer Hospital & Institute, Beijing, China; The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Zhongshan Hospital, Fudan University, Shanghai, China; Hunan Cancer Hospital, Changsha, Hunan, China; Zhejiang Hospital, Zhejiang University School of Medicine, Hangzhou, China; Shandong Cancer Hospital, Jinan, China; Fujian Cancer Hospital, Fuzhou, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Fujian Medical University Union Hospital, Fuzhou, China; Akeso Biopharma, Inc., Zhongshan, China

Background: Anti-PD-1 monoclonal antibodies plus chemo as first-line therapy for advanced G/GEJ cancer yields OS and PFS benefits compared to chemo alone while the survival benefits are limited, especially in patients with low PD-L1 expression (CPS <5). Simultaneous blockade of the PD-1 and CTLA-4 pathways has shown synergistic anti-tumor activity and has been proven effective across multiple cancer types. This phase Ib/II dose-escalation study evaluated the safety and efficacy of AK104, a PD-1/CTLA-4 bispecific antibody, combined with XELOX or modified XELOX (mXELOX) in the first-line treatment of G/GEJ cancer cohorts (NCT03852251).

Methods: Pts with unresectable advanced G/GEJ adenocarcinoma and no prior systemic therapy, regardless of PD-L1 status, were enrolled, excluding known HER2-positive pts. Enrolled patients received AK104 (4 mg/kg, 6 mg/kg or 10 mg/kg Q2W, 10 mg/kg or 15 mg/kg Q3W) + chemo (mXELOX Q2W or XELOX Q3W). The primary endpoint was safety and the objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

Results: As of 31 Oct. 2022, 98 pts were enrolled with only 4 pts in 10 mg/kg Q3W, the safety and efficacy of the regimen of 10mg/kg Q3W will be reported in the phase III study and not be reported here. 94 pts were enrolled with median age of 62.7 years (range: 29–75), 70.2% male, 62.8% ECOG PS 1, and 45.7% liver metastasis. The median follow-up was 24.0 months (range: 0.5–33.3). 88 patients (94%) had at least one post-baseline tumor evaluation. The ORR was 68.2% (60/88), with 5 (5.7%) complete responses and 55 (62.5%) partial responses. The disease control rate (DCR) was 92.0% (81/88). The median duration of response (DoR) was 9.69 months (95%CI, 5.82 to 14.00). The median PFS was 9.20 months (95%CI, 6.67 to 10.48). The median OS was 17.41 months (95%CI, 12.35 to 29.77). In pts with PD-L1 CPS <5 and CPS ≥5, the median OS was 20.24 months and 17.28 months, respectively. Treatment-related adverse events (TRAEs) occurred in 97.9% of pts. The most frequent were platelet count decreased (62.8%), white blood cell count decreased (61.7%), neutrophil count decreased (59.6%), anemia (51.1%), aspartate aminotransferase increased (33.0%), nausea (30.9%), and vomiting (30.9%). Grade ≥3 TRAEs occurred in 69.4% of pts. No new safety signals were identified. Conclusions: AK104, combined with mXELOX/XELOX, showed promising activity and manageable safety in previously untreated patients with advanced G/GEJ adenocarcinoma. AK104 + chemo represents a potential new first-line treatment option for these pts. A phase III study of AK104 combined with chemo as first-line therapy for G/GEJ cancer is underway (NCT05008783). Clinical trial information: NCT03852251. Research Sponsor: Akeso Biopharma, Inc.
Ramucirumab, avelumab and paclitaxel (RAP) as second line treatment in esophagogastric adenocarcinoma: Final results of the phase 2 RAP trial (AIO-STO-0218).

Peter C. Thuss-Patience, Anica Högener, Eray Goekkurt, Michael Stahl, Albrecht Kretzschmar, Thorsten Oliver Goetze, Gertraud Stocker, Peter Reichardt, Frank Kullmann, Daniel Pink, Prisca Bartels, Armin Jarosch, Axel Hinke, Lisa Paschold, Alexander Stein, Mascha Binder; Charité University Medicine Berlin, Department of Haematology, Oncology and Cancer Immunology, Campus Virchow-Klinikum, Berlin, Germany; Charité–University Medicine Berlin, Department of Haematology, Oncology and Cancer Immunology, Campus Virchow-Klinikum, Berlin, Germany; Hematology Oncology Practice Eppendorf and University Cancer Center Hamburg (UCCH), Hamburg, Germany; Evang. Kliniken Essen-Mitte, Klinik für Internistische Onkologie und Hämatologie, Essen, Germany; Hematology and Oncology Practice MVZ Mitte, Leipzig, Germany; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany; University Cancer Center Frankfurt, Frankfurt, Germany; University Cancer Center Leipzig, Leipzig, Germany; Sarcoma Center Berlin-Brandenburg, Helios Klinikum Berlin Buch, Berlin, Germany; Klinikum Weiden, Weiden, Germany; Helios Klinikum Bad Saarow-Sarcoma Center Berlin-Brandenburg and University Medicine Greifswald, Bad Saarow, Germany; Charité - University Medicine Berlin, Institute of Pathology, Berlin, Germany; CCRC Cancer Clinical Research Consulting, Düsseldorf, Germany; Department of Internal Medicine IV, University Hospital Halle, Martin-Luther University Halle-Wittenberg, Halle, Germany

Background: The addition of immune checkpoint inhibitors to chemotherapy has improved outcomes in patients (pts) with metastatic esophagogastric adenocarcinoma (EGA), but treatment combinations and optimal pt selection need to be established. Objective: To investigate efficacy and tolerability of the programmed death-ligand 1 (PD-L1) inhibitor avelumab with ramucirumab and paclitaxel in the second line treatment of pts with metastatic EGA (NCT03966118).

Methods: In this phase 2 multicenter single-arm clinical trial the reported results are based on a median follow-up of 27.4 months. Patients with previously treated metastatic EGA, adequate organ function, and eligibility for immunotherapy were included. Interventions: Pts with metastatic EGA after progression on platinum/fluoropyrimidine based palliative first line treatment, checkpoint-inhibitor naive, received ramucirumab 8 mg/kg (d1,15), avelumab 10 mg/kg (d1,15) and paclitaxel 80 mg/m² (d1,8,15) q4w.

Results: The pre-specified primary end point was overall survival rate at 6 months (mo) (H0 $\leq$50%, H1 $\geq$65%). A total of 60 patients (pts) were enrolled, 59 were evaluable (intention to treat, ITT). Participants had a median age of 64.0 yrs (range 18-81) and 80% were men. Baseline Eastern Cooperative Oncology Group performance status was 0 in 23 pts (39.0%) and 1 in 36 pts (61.0%); 29 pts (48.2%) had EGA localized in the esophagogastric junction and 30 in the stomach (51.8%). all pts had received prior platin/5-FU based chemotherapy, 40pts (67.8%) had prior taxanes. Central post-hoc biomarker analysis (56 pts) showed PD-1 ligand 1 (PD-L1) combined positive score of 5 or greater in 24 pts (42.9%). The observed overall survival (OS) rate at 6 mo was 71% (95% CI 61-84%) and at 12 mo 43% (95% CI 32-58%). The median OS (ITT) was 10.6 mo (95% CI 8.4-12.8); 9.4 mo (95% CI 7.2-11.7) in pts with PD-L1 CPS $\geq$5 and 14.0 mo (95% CI 6.0-22.1; p = 0.25) in those with PD-L1 CPS $<5$. Treatment was generally well tolerated without unexpected toxicities. Translational research identified subgroups with a longer survival possibly due to a higher treatment benefit. Pts with higher than median T cell repertoire (TRB) richness showed an elevated median OS of 20.4 mo compared to pts with lower than median TRB richness (med OS 8.3 mo; HR 0.43, 95% CI 0.23-0.81; p = 0.0079). Pts with lower than median cfDNA burden had a median OS of 19.2 mo compared to pts with higher than median cfDNA (med OS 7.3 mo; HR 0.30, 95% CI 0.16-0.59; p = 0.0022).

Conclusions: In this multicenter clinical trial, ramucirumab and paclitaxel combined with avelumab showed favorable efficacy and tolerability in the second line treatment of pts with metastatic EGA. PD-L1 CPS $\geq$ 5, cfDNA below the median or T cell richness above the median seem to predict for even better outcomes with median OS hardly seen before in the second line setting. Clinical trial information: NCT03966118. Research Sponsor: Financially supported by Merck Healthcare KGaA, Darmstadt, Germany, (CrossRef Funder ID: 10.13039/100009945) as part of an alliance between the healthcare business of Merck KGaA and Pfizer.
EpCAM CAR T (IMC001) for the treatment of advanced GI cancers.

Tianhang Luo, Weijia Fang, Zhengmao Lu, Chuchu Tong, Hangyu Zhang, Guoqiang Ai, Suqiong Wang; Shanghai Changzhai Hospital, Shanghai, Shanghai, China; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; The First Affiliated Hospital of ZheJiang University, Hangzhou, China; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; Suzhou Immunofoco Biotechnology Co., Ltd, Suzhou, Jiangsu, China

Background: EpCAM is highly expressed in various cancer types of the GI system and at metastatic sites. It serves as a promising prognostic/predictive marker (CTC) and therapeutic target. IMC001 is an EpCAM-targeted CAR-T cell that showed promising anti-tumor activities in preclinical studies. Here, we report the results of the low and middle dosage groups in advanced gastric cancers (CT03) and GI cancers (CT04). Methods: This first-in-human, open-label trial involved two separate single-site trials. Both followed a classic 3+3 design with dose escalation of 0.3, 1 or 3 million CAR-T cells/kg after lymphodepletion chemotherapy. CT03 was an IMC001 monotherapy trial (Stage 1) for gastric cancer, while CT04 had Stage 1 and the combination with RFA or microwave ablation (Stage 2) for GI cancers. Eligible patients were those with EpCAM-positive (more than 10%) cancers who had no further standard treatment options and were ECOG 0 or 1. The objective was to assess the safety, PK/PD profile and preliminary efficacy of IMC001. Results: As of January 30, 2023, 12 patients with 6 colorectal and 6 gastric cancers had enrolled, with half receiving 0.3 million and the other half receiving 1 million cells/kg IMC001 infusion. No patient experienced DLT within the 4-week follow-up visits after infusion. All patients experienced ≥Grade 3 hematologic toxicity. One patient in the low-dose group had a SAE of immune hepatitis (Grade 3), which might have been related to cell therapy, and occurred around 11 days after the CAR-T infusion, prolonging the patient’s hospitalization. Manageable CRS (Grade 1 to 3) and no ICANS were observed. Other adverse events related to cell therapy were CTCAE Stage 1-2 nausea, vomiting, asthenia, or pruritus, and these recovered quickly. Analyses of the CAR-T cells in peripheral blood revealed robust engraftment in all patients, with the peak number of CAR+ cells reaching on day 5-7 after infusion. CTC remained under the detection limit for more than 40 weeks after cell infusion. Significant elevations of serum levels of IL-6, IP-10, IFN-γ, IL-15, and MCP-1 were observed in most patients. Preliminary efficacy data showed that 2 out of 6 advanced gastric cancer patients were evaluated as PR and 3 remained SD by RECIST 1.1 at the low and middle dosages (CT03). The first PR patient received a second IMC001 infusion on week 50 and had survived for more than 60 weeks. The second PR patient underwent successful surgical removal of the stomach 28 weeks after IMC001 infusion. The CT04 trial is ongoing. Conclusions: This is the first CAR-T therapy ever tested in humans targeting the EpCAM. IMC001 showed a favorable safety profile and reasonable anti-tumor activities at the low and middle dosage levels in patients with advanced EpCAM+ GI cancers, especially in gastric cancer. In addition, our trial has successfully provided a surgical treatment opportunity after CAR-T therapy downstaging of unresectable gastric cancers. Updated data from open cohorts will be presented. Clinical trial information: NCT05028933. Research Sponsor: Suzhou Immunofoco Biotechnology Co., Ltd.
Global prevalence of CLDN18.2 in patients with locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Biomarker analysis of two zolbetuximab phase 3 studies (SPOTLIGHT and GLOW).

Kohei Shitara, Rui-Hua Xu, Diarmuid Martin Moran, Abraham Guerrero, Ran Li, Janet Pavese, Maria Matsangou, Pranob P. Bhattacharya, Jaffer A. Ajani, Manish A. Shah; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; Astellas Pharma Global Development, Inc., Northbrook, IL; Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Weill Cornell Medical College, New York, NY

Background: There is an unmet need for additional therapies to treat patients (pts) with locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma. Claudin-18.2 (CLDN18.2), a new validated target in these pts, is expressed in normal gastric mucosa cells and often retained in G/GEJ tumor cells. There are limited data on the global prevalence of CLDN18.2 in tumors of pts with LA unresectable or mG/GEJ adenocarcinoma. The SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) phase 3 studies demonstrated clinically meaningful and statistically significant improvement in PFS and OS with the CLDN18.2-targeted antibody zolbetuximab + chemotherapy (mFOLFOX6 or CAPOX, respectively) vs placebo + chemotherapy as 1L therapy in pts with CLDN18.2+/HER2− disease. We report the biomarker analysis of these studies.

Methods: Pts with LA unresectable or mG/GEJ adenocarcinoma were screened for CLDN18.2 status by IHC before enrollment. Tumors were defined as CLDN18.2+ if they had ≥75% of tumor cells with moderate-to-strong membranous CLDN18 staining per the investigational VENTANA CLDN18 (43-14A) RxDx Assay. HER2 status was evaluated per central or local assessment. Ad hoc PD-L1 IHC was performed via the Dako PD-L1 IHC 28-8 pharmDx assay for a subgroup of enrolled pts. Results exclude pts from mainland China and pts missing data for disease type, Lauren classification, or tumor collection site.

Results: Across SPOTLIGHT and GLOW, 3576 pts had valid CLDN18 IHC results; 1399 (39.1%) had CLDN18.2+ tumors. CLDN18.2 prevalence was 43.7% (513/1175) in female pts and 36.9% (886/2401) in male pts. CLDN18.2 prevalence was 44.0% (671/1524) in pts in Europe/Middle East, 37.7% (183/485) in pts in N. America, and 36.5% (479/1314) in pts in Asia Pacific. CLDN18.2 prevalence was 41.0% (1056/2576) in pts with gastric adenocarcinoma and 37.3% (302/809) in pts with GEJ adenocarcinoma. CLDN18.2 prevalence trended higher in pts with diffuse (48.9%, 479/980) vs intestinal (38.9%, 265/682) disease. CLDN18.2 prevalence was 41.1% (175/426) in tumors collected from metastatic sites and 38.6% (1195/3094) in tumors collected from primary sites. CLDN18.2 prevalence was similar across other clinical and histopathological characteristics. Of 2908 HER2− pts with valid CLDN18 IHC results, 1264 (43.5%) had CLDN18.2+ tumors. Of 599 enrolled pts tested for PD-L1 expression, 104 (17.4%) had a PD-L1 CPS ≥5. Conclusions: The SPOTLIGHT and GLOW phase 3 studies are the largest data sources to date for determining global CLDN18.2 prevalence. CLDN18.2 is a high prevalence biomarker, with high tumor expression in ~35–40% of pts with LA unresectable or mG/GEJ adenocarcinoma, for whom zolbetuximab + chemotherapy represents a potential 1L therapy. Clinical trial information: NCT03504397, NCT03653507. Research Sponsor: Astellas Pharma Global Development, Inc.
Cell free DNA (cfDNA) assessment of esophagogastric (EG) cancer using MSK-ACCESS.

Samuel Louis Cytryn, David B. Solit, Henry S. Walch, Walid Khaled Chatila, Steven Brad Maron, Efsevia Vakiani, Angela Rose Brannon, Marc Ladanyi, Nikolaus Schultz, Michael F. Berger, Yelena Y. Janjigian; Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY

Background: The incidence of EG cancer is rising, the treatment paradigm is increasingly complex, and the role of predictive biomarkers is critical in selecting optimal therapies. Therefore, longitudinal, non-invasive methods to characterize dynamic tumor molecular profiles, such as cfDNA, are needed.

Methods: Patients with EG cancer receiving care at Memorial Sloan Kettering (MSK) had cfDNA analysis with an ultrasensitive capture based liquid biopsy for detection of somatic alterations in 129 cancer associated genes (MSK ACCESS). Tumor samples were analyzed with MSK-IMPACT, a capture based next generation sequencing (NGS) platform. Results: 100 patients with EG adenocarcinoma underwent cfDNA analysis to evaluate for molecular residual disease with MSK ACCESS. 85 (85%) had tissue NGS with MSK IMPACT. Median TMB was 5.3 mut/Mb (IQR 2.6-7.4) and median number of alterations per sample was 11 (IQR 7-17). 71% had TP53 mutations and 22% had an ERBB2 amplification (amp). 79 (79%) patients had cfDNA obtained prior to treatment (50 [63%] metastatic disease; 29 [37%] localized disease) and 21 (21%) at the time of progression. Alterations were detectable on cfDNA more frequently in patients with later stage disease (p=0.031) and fewer alterations per sample were detected compared to tissue NGS (mean difference 14, 95% CI 10-18, p<0.001). The most common were TP53 (62%), CDKN2A (12%), PIK3CA (10%), ARID1A (10%), and ATM (10%). TP53 was detected with increasing frequency in patients with later stage disease (p=0.004). However, amplifications, which included ERBB2, MYC, EGFR, and FGFR2, were detected exclusively in those with stage IV disease (p=0.005) and cfDNA was less sensitive in detecting amplifications compared to tissue NGS (p<0.001). This is notable as HER2 positivity is determined in part by ERBB2amp. 25 of 30 HER2+ patients had both tissue NGS and cfDNA. 19 (76%) had ERBB2amp on tissue NGS and only 8 (32%) had ERBB2amp on cfDNA (p=0.004). Additionally, copy number was lower on cfDNA compared to tissue NGS (mean difference 13, 95% CI 1.3-24.9, p=0.02) and IHC 3+ tumors were more likely to have ERBB2amp detected than IHC 2+ tumors (p=0.049). However, alterations along the MAPK, PI3K, WNT, and TGF-β pathways, which are associated with trastuzumab resistance and poor survival, were detected with similar frequency on both platforms (40 v 32%, p=0.77).

Conclusions: Our findings in this large prospective analysis highlight the utility of cfDNA with MSK ACCESS as a complimentary tool for molecular characterization in patients with EG cancer. cfDNA in EG cancer. Research Sponsor: Memorial Sloan Kettering Cancer Center.
Effect of autologous lymphocytes combined with chemotherapy as the first-line treatment of advanced gastric cancer.

Xiaoting Ma, Lin Yang; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China

**Background:** To evaluate the safety and initial efficacy of adoptive cell therapy (ACT) combined with SOX in first-line treatment of locally advanced unresectable or metastatic gastric adenocarcinoma/gastroesophageal adenocarcinoma. **Methods:** In this single-arm, single-center exploratory trial, patients with histologically confirmed locally advanced unresectable or metastatic gastric adenocarcinoma/gastroesophageal adenocarcinoma were randomly assigned (1:1) to receive ACT in combination with S-1 and oxaliplatin (SOX) or SOX alone. The primary endpoint was the incidence of adverse events (AEs). Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR). **Results:** Fifty-nine patients were enrolled in the study between November 20, 2014 and September 6, 2017. 31 patients received ACT combined with SOX (ACT-SOX) and 28 patients received SOX. The most common AEs in both groups were gastrointestinal reaction, leucopenia, neutropenia, anemia, thrombocytopenia, hyperbilirubinemia and elevated aspartate transaminase concentration, with a higher incidence in the SOX group. The median PFS for ACT-SOX and SOX were 6.9 and 4.9 months respectively (HR 0.80, p=0.45), and the median OS were 17.8 and 9.75 months (HR 0.76, p=0.34). Patients who received more than three injections of specific lymphocyte subsets benefited the most from combination therapy. Cox univariate and multivariate analysis showed that tumor metastasis to more than two organs was the main risk factor for PFS and OS. 29 patients in the ACT-SOX group and 25 in the SOX group had measurable lesions. The ORR of ACT-SOX group and SOX group was 55.2% and 32.0%, and DCR of two groups was 93.1% and 88.0%. **Conclusions:** The safety of ACT-SOX in first-line treatment of patients with locally advanced unresectable or metastatic gastric adenocarcinoma/gastroesophageal adenocarcinoma is good. Compared with SOX alone, although the PFS and OS of ACT-SOX did not reach statistical difference, it could further extend the time of PFS and OS, and the absolute improvement time of OS was about 8.05 months. Continuous benefit of ACT-SOX was observed through long-term follow-up. Clinical trial information: NCT02504229. Research Sponsor: None.
Health-related quality of life (HRQOL) in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC) or esophageal adenocarcinoma (EAC): 36-month results of nivolumab plus chemotherapy (N+C) versus (C) from CheckMate 649.

Elena Elimova, Lucjan Wyrwicz, Clara Chen, Steven Michael Blum, Eric Davenport, Jinyi Wang, Kaoru Kondo, Markus H. Moehler; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; Bristol Myers Squibb, Princeton, NJ; RTI Health Solutions, Research Triangle Park, NC; Bristol-Myers Squibb Research, Princeton, NJ; Department of Medicine, Johannes-Gutenberg University Clinic, Mainz, Germany

Background: CheckMate 649 (NCT02872116) is a randomized, open-label, phase 3 study in first-line treatment of pts with advanced GC/GEJC/EAC. Primary results showed statistically significant improvement in overall survival (OS) for N+C versus C in all randomized pts. Prior analyses conducted for 24-month follow-up (FUP) showed pts receiving N+C maintained HRQOL and experienced delayed deterioration in HRQOL compared with pts receiving C. Here we report additional analyses of HRQOL with 36-month FUP data. Methods: Functional Assessment of Cancer Therapy–Gastric Cancer (FACT-Ga) and EQ-5D-3L results were collected at baseline (BL) and every 6 weeks while on treatment. Change from BL in FACT-Ga, EQ-5D Visual Analog Scale (VAS), and Utility Index (UI) scores were analyzed using mixed models. Time to first symptom deterioration (TTSD), time until definitive deterioration (TuDD), and time to improvement (TTI) were estimated with Kaplan-Meier estimators and stratified Cox models; deterioration/improvement events were based on prespecified meaningful thresholds for change scores. Results: A total of 1,581 pts were randomized to N+C (n = 789) and C (n = 792); of those, 1,360 pts had BL and post-BL PROs and were included in the PRO population (N+C [n = 694] and C [n = 666]). With additional follow-up, least-squares mean differences from BL remained comparable between groups across visits for HRQOL measurements with exceptions. FACT-Ga total score, GaCS, physical well-being (WB), and emotional WB tended to favor N+C; social WB tended to favor C. For all randomized pts, most time-to-event endpoints favored N+C; like the 24-month analysis, statistically significant delays in deterioration were maintained for TuDD (except FACT-G Social WB) and TTSD (only FACT-GaCS and FACT-Ga total). Conclusions: These results confirm the earlier 24-month FUP findings. Compared with C alone, N+C maintained HRQOL with decreased risk of deterioration in pts with previously untreated advanced or metastatic GC/GEJC/EAC. Together with improved OS, data continue to support N+C as a first-line standard treatment for GC/GEJC/EAC. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.

<table>
<thead>
<tr>
<th>Instrument/Scale</th>
<th>TTSD HR (95% CI)</th>
<th>TuDD HR (95% CI)</th>
<th>TTI HR (95% CI)</th>
</tr>
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<tr>
<td>Physical WB</td>
<td>0.90 (0.77-1.05)</td>
<td>0.78 (0.64-0.95)</td>
<td>1.06 (0.88-1.27)</td>
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<tr>
<td>Social WB</td>
<td>0.96 (0.81-1.13)</td>
<td>0.88 (0.71-1.09)</td>
<td>0.98 (0.80-1.20)</td>
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<td>Emotional WB</td>
<td>1.04 (0.86-1.26)</td>
<td>0.75 (0.59-0.97)</td>
<td>0.98 (0.84-1.15)</td>
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<td>Functional WB</td>
<td>0.94 (0.80-1.11)</td>
<td>0.69 (0.56-0.86)</td>
<td>1.08 (0.92-1.27)</td>
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<tr>
<td>FACT-G Total</td>
<td>0.92 (0.77-1.08)</td>
<td>0.72 (0.59-0.89)</td>
<td>0.93 (0.79-1.10)</td>
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<tr>
<td>GaCS Subscale</td>
<td>0.78 (0.64-0.95)</td>
<td>0.73 (0.57-0.94)</td>
<td>1.01 (0.86-1.18)</td>
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<tr>
<td>FACT-Ga Total</td>
<td>0.82 (0.67-0.99)</td>
<td>0.71 (0.55-0.91)</td>
<td>1.07 (0.91-1.26)</td>
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<td>EQ-5D UI (UK set)</td>
<td>0.86 (0.73-1.01)</td>
<td>0.75 (0.61-0.91)</td>
<td>1.14 (0.97-1.33)</td>
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<td>EQ-5D VAS</td>
<td>0.87 (0.75-1.02)</td>
<td>0.78 (0.64-0.94)</td>
<td>1.12 (0.96-1.31)</td>
</tr>
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</table>

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Survival analysis by tumor response of nivolumab treatment in previously treated advanced gastric cancer from the DELIVER trial (JACCRO GC-08).

Yu Sunakawa, Yasuhiro Sakamoto, Ryohei Kawabata, Atsushi Ishiguro, Yusuke Akamaru, Yosuke Kito, Masazumi Takahashi, Jin Matsuyama, Hiroshi Yabusaki, Akitaka Makiya, Takahisa Suzuki, Masahiro Tsuda, Hisateru Yasui, Jun Hihara, Atsushi Takeno, Eisuke Inoue, Wataru Ichikawa, Masashi Fuji; Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan; Department of Medical Oncology, Osaki Citizen Hospital, Osaki, Japan; Department of Surgery, Sakai City Medical Center, Sakai, Japan; Department of Medical Oncology, Taisei Keijinkai Hospital, Sapporo, Japan; Department of Gastrointestinal Surgery, Ikeda City Hospital, Ikeda, Japan; Department of Medical Oncology, Ishikawa Prefectural Central Hospital, Ishikawa, Japan; Division of Gastroenterological Surgery, Yokohama Municipal Citizen’s Hospital, Yokohama, Japan; Department of Gastroenterological Surgery, Higashiosaka City Medical Center, Higashi Osaka City, Japan; Department of Gastroenterological Surgery, Niigata City Cancer Center Hospital, Niigata, Japan; Cancer Center, Gifu University Hospital, Gifu, Japan; Department of Surgery, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure, Japan; Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi, Japan; Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan; Department of Surgery, Hiroshima City Asa Hospital, Hiroshima, Japan; Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan; Showa University Research Administration Center, Showa University, Tokyo, Japan; Division of Medical Oncology, Showa University Fujigaoka Hospital, Yokohama, Japan; Japan Clinical Cancer Research Organization, Tokyo, Japan

Background: We conducted a prospective observational study, DELIVER trial (UMIN000030850), to evaluate the real-world effectiveness of nivolumab monotherapy in previously treated advanced gastric cancer (GC) and have reported comparable efficacy and safety data (Takahashi, et al. Gastric Cancer 2021). There are few evidence regarding the association between tumor response and survival time in later-line treatment with nivolumab alone for advanced GC. We therefore report results from post-hoc exploratory analyses of survival time by tumor response from the DELIVER trial. Methods: The DELIVER trial enrolled 501 patients (pts) with advanced gastric or GEJ adenocarcinoma treated with nivolumab alone. Primary endpoint was overall survival (OS), secondary endpoints were response rate (RR), disease control rate, progression-free survival (PFS), tumor shrinkage rate / tumor progression rate at 1st evaluation, tumor growth rate, and safety. The exploratory analyses were performed for survival according to tumor response and depth of response (DpR) in pts with measurable lesions who were receiving nivolumab as 3rd or later-line treatment. The survival data was fixed at the timepoint of 2 years after the last enrollment. Results: 234 pts were evaluable (median age 70y [26-90], 79% male, ECOG PS0/1/2 46/43/11%, 32% pts with ascites). Median OS was 6.5 months (95%CI 5.3-8.2) and median PFS was 1.8 months (95%CI 1.6-2.0). The RR was 15.0% (95%CI 10.4-19.5) with 5 complete response (CR) and 30 partial response (PR). The median PFS and OS were not reached for pts with CR, 11.7 and 29.8 months for pts with PR, 3.8 and 11.4 months for pts with stable disease, and 1.5 and 4.2 months for pts with progressive disease, respectively. In addition, the median DpR was -14.1% and was associated with PFS and OS in the Spearman analysis (r=0.55 and r=0.44, respectively). When the DpR was divided into 5 groups according to tumor shrinkage, there was difference in PFS and OS. Conclusions: This exploratory analysis indicated the association between DpR and survival time in pts with advanced GC treated with nivolumab alone in later-line. Increasing DpR was associated with longer median PFS and OS. Clinical trial information: UMIN000030850. Research Sponsor: Ono Pharmaceutical and Bristol-Myers Squibb.
Ultra-sensitive, tumor-informed ctDNA profiling in patients with gastroesophageal cancer and treated with pembrolizumab and longitudinal ctDNA kinetics.

Andrew B. Nixon, Lee McDaniel, Jingquan Jia, Charles Abbott, Lauren Howard, John C. Brady, Katherine I. Zhou, Donna Niedzwiecki, Richard Chen, John H Strickler, Sean Michael Boyle, Hope Elizabeth Uronis; Duke University Medical Center, Durham, NC; Personalis, Inc., Menlo Park, CA; University of North Carolina at Chapel Hill, Chapel Hill, NC; Duke University, Durham, NC

Background: Metastatic esophagogastric cancer (mEGC) is a lethal disease with poor long-term survival. Recent studies have established anti-PD-1 therapy in combination with chemotherapy as the standard of care for first-line therapy for mEGC. KeyLargo (NCT03342937) was a single arm phase II study of pembrolizumab in combination with oxaliplatin and capecitabine in the first line treatment of patients (pts) with HER2 negative mEGC. While high response rates were noted, not all pts received benefit, emphasizing the need for better biomarkers. Paired tumor biopsies and plasma were collected for optimal biomarker testing. In this retrospective study, we employed a novel, tumor-informed ctDNA approach as a tool for longitudinal disease monitoring and dynamic tumor evolution.

Methods: Thirty-six pts were enrolled between January 2018 and January 2020. Of 34 evaluable pts, 25 pts achieved a response (ORR = 74%), including 6 pts with a complete response (CR) and 19 pts with a partial response (PR). Our initial analysis includes baseline tumor samples collected from 16 pts with over 59 corresponding on-treatment (OT; up to cycle 35) plasma samples. NeXT Personal, a tumor-informed ctDNA assay, generated personalized liquid biopsy panels derived from somatic variants (SV) from tumor whole genome sequencing. Each personalized assay includes up to 1,800 SVs for sensitive minimal residual disease (MRD) detection and a constant set of 2,100 clinically actionable variants (CAV).

Results: Of the 36 pts who enrolled on KeyLargo, 32 pts had baseline tumor and longitudinal plasma samples collected and stored for testing. In the initial cohort of 16 pts, MRD events dynamically varied from 5.3 to 302,000 parts per million (PPM). 16/16 (100%) pts were MRD-positive at baseline, with a limit of detection between 1.5 and 4.6 PPM. OT samples were collected every 3 cycles (9 weeks). The ratio of PPM (rPPM) between baseline and the first available OT sample (typically Cycle 4 to 7) correlated with progression free survival (PFS; p = 0.0004, logrank). rPPM was significantly reduced in pts having a best overall response of PR/CR (98% mean rPPM) versus progressive disease (25% mean rPPM, p < 0.037, U-test). Two pts demonstrated CR, each with 11/11 (100%) MRD-negative plasma samples over approximately two years. CAVs were identified in longitudinal samples with TP53 repeatedly detected in 5 patients and a PIK3CA mutation emerging in the final 3 (of 9) timepoints from one patient. Conclusions: ctDNA was present in all pts at baseline; OT PPM reductions correlated with PFS and best overall response. CAV profiling suggested a de novo PIK3CA variant arising during therapy in one patient. These findings suggest that tumor-informed plasma-based ctDNA profiling in mEGC may detect known CAVs arising during therapy, and with subsequent investigations, may inform therapeutic decisions. Research Sponsor: Personalis, Inc.
Updated results of anlotinib combined with TQB2450 (PD-L1 blockade) as first-line treatment for advanced esophageal squamous cell carcinoma (ESCC): A single-arm, multicenter, open-label phase II clinical trial.

Zhiye Zhang, Xiangrui Meng, Xiuli Yang, Yong-Gui Hong, Jin Xia, Yunfang Chen, Tao Wu, Zheng-Zheng Shan, Qingxia Fan, Feng Wang; The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Nanyang Medical College First Affiliated Hospital, Nanyang, China; Anyang Tumor Hospital, Anyang, China; Anyang Tumor Hospital, Anyang, Henan, China; Zhumadian Central Hospital, Zhumadian, China

Background: PD-1 blockades combined with chemotherapy in first-line setting exhibited encouraging efficacy for patients with ESCC recently. However, the safety profile of conventional chemotherapy was still disappointing. Therefore, the chemotherapy-free regimen might be a promising strategy. As a novel multitarget TKI mainly targeting VEGFR1-3, anlotinib was a potential first-line combination therapy and second-line monotherapy for patients with ESCC in China. TQB2450 was a novel PD-L1 blockade developed by Chia Tai Tianqing Pharmaceutical Group Co., Ltd. (Nanjing, China). Therefore, this study was designed to explore the efficacy and safety of anlotinib combined with TQB2450 as first-line therapy in advanced ESCC. The preliminary results were reported in 2023 ASCO-GI Symposium (Abs 377) and the update results were reported here.

Methods: Patients with previously untreated metastatic or locally advanced ESCC, whose age was between 18 and 75 years, with ECOG PS of 0 or 1 and life expectancy of >3 months were eligible as the inclusion criteria. Eligible patients were administered with anlotinib (12mg, po, d1~14, q3w) plus TQB2450 (1200mg, iv, d1, q3w) until disease progression or unacceptable toxicity. The tumor response was assessed according to RECIST 1.1 and iRECIST using CT scans every 2 cycles for the first 6 cycles, and every 3 cycles thereafter. Adverse events were recorded by severity in accordance with the NCI CTC AE Version 5.0. The predefined sample size was 46. The primary endpoint was ORR. Secondary endpoints included safety, PFS, DCR, DoR and OS.

Results: From Mar 2022 to Sep 2022, a total of 46 patients were enrolled. At the data cut-off date (Dec, 2022), there were 1 CR (2.2%), 27 PR (58.7%), 14 SD (30.4%) and 4 NE (8.7%). Therefore, the preliminary ORR was 60.9% (95%CI: 45.4%~74.9%), DCR was 91.3% (95%CI: 79.2%~97.6%). The median PFS of the 46 pts was not yet available. Additionally, safety profile exhibited that the regimen was tolerable. The most common treatment-related adverse events in 46 patients with the incidence >10% were hypertension (28%), hypothyroidism (20%), leukocytosis (20%), hyperthyroidism (17%), anemia (15%), fatigue (15%), neutrophil count decreased (11%), constipation (11%), sinus bradycardia (11%) and hand-foot syndrome (11%). The common grade $\geq$3 treatment-related adverse events were hypertension (4%), hand-foot syndrome (2%), hyponatremia (2%), platelet count decreased (2%) and lymphocyte count decreased (2%).

Conclusions: Preliminary results suggested that anlotinib combined with TQB2450 as first-line therapy in advanced ESCC exhibited encouraging efficacy and manageable adverse events. And the conclusions needed to be confirmed in trials continued subsequently. Clinical trial information: NCT05038813. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.
Phase II study of lenvatinib plus pembrolizumab for patients with immunotherapy-naive advanced gastric cancer following first line therapy.

Deirdre Jill Cohen, Jonathan W Lee, Daniel Jacob Becker, Despina Siolas, Nina Beri, Theresa Ryan, Peter Kozuch, Shun Yu, Benjamin A. Levinson, Judith D. Goldberg, Lawrence P. Leichman, Paul Eliezer Oberstein; Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY; Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY; NYU, New York, NY; NYU Grossman School of Medicine, Department of Population Health, Division of Biostatistics, New York, NY; New York University School of Medicine, New York, NY

Background: Immune checkpoint inhibitor (ICI) therapy has demonstrated efficacy in some patients (pts) with advanced gastric cancer (AGC) and is now approved in 1st line combination with chemotherapy. Preclinical studies suggest interplay between angiogenesis and the immune system, with VEGF exerting effects on the anti-tumor immune response including antigen presentation, effector mechanisms and immune cell trafficking. We hypothesized that the combination of VEGF inhibition and ICI may be more beneficial than either agent alone. We designed an open-label prospective phase II trial to evaluate the efficacy of lenvatinib (Len) plus pembrolizumab (Pem) beyond first line therapy in ICI-naive AGC. Methods: Eligible pts included advanced gastric or gastroesophageal adenocarcinoma regardless of PD-L1 status, with measurable disease per RECIST 1.1, ECOG ≤1, and progressive disease on ≥1 prior regimen, no prior ICI. Pts received an initial lead-in week of Len 20mg PO daily which was then continued in combination with Pem 200mg IV every 3 weeks from day 8. Therapy was continued until progression or intolerance. Imaging was performed every 6 wks for the first 12 wks and then every 9 wks. Primary end point was objective response rate (ORR). Using the Simon optimal 2 stage design, planned sample size was 29 patients (pts) with 80% power and one-sided alpha of 5%. The study would be considered positive if ≥6 pts achieved an objective response. Secondary endpoints included safety and tolerability, PFS and OS. Results: During the course of this study, ICI was approved in the 1st line setting and as a result of changing practice patterns, enrollment was prematurely suspended in 7/2022 with 24 of 29 planned pts. All enrolled pts were included for the safety analysis. All subjects were mismatch repair proficient, 15 pts (62.5%) were CPS positive (≥1), data was missing for 1 pt. 19 pts who completed at least 2 cycles were evaluable for response; 15 were treated in 2nd line and 4 in 3rd line. Five pts (21%) had a partial response, including 1 with CPS=0 and 1 with CPS=1. Median PFS and OS was 12.9 and 21.4 weeks for the entire cohort. The combination was generally tolerable without new safety signals. Dose reductions were required in 3 (13%) pts, overall compliance with len was 79% of planned doses across the study. Eleven (46%) pts experienced at least one G3 toxicity and one (4%) pt experienced G4 toxicity. Most common G3 toxicities included fatigue (27%), anorexia (18%), lymphopenia (18%), and hyperbilirubinemia (18%). Conclusions: Lenvatinib combined with pembrolizumab was well tolerated, responses were seen, but the study did not meet the primary endpoint in ICI naïve AGC. Given the changing landscape of care, ICI is now more broadly used in first line therapy, additional studies are warranted to determine the role of this combination in ICI exposed pts. Clinical trial information: NCT03321630. Research Sponsor: Eisai; Merck; U.S. National Institutes of Health.
Efficacy of ramucirumab combination chemotherapy as second-line treatment in patients with advanced adenocarcinoma of the stomach or gastroesophageal junction after exposure to checkpoint inhibitors and chemotherapy as first-line therapy within the prospective phase II IKF-S628/AIO-STO-0417 (MOONLIGHT) trial.

Michael Masetti, Salah-Eddin Al-Batran, Peter C. Thuss-Patience, Jorge Riera-Knorrenschild, Eray Goekkurt, Gunnar Folprecht, Thomas Jens Ettrich, Udo Lindig, Kim Barbara Luley, Daniel Pink, Tobias Nicolaas Dechow, Disorn Sookthai, Sabine Junge, Claudia Pauligk, Sylvie Lorenzen; Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, and Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt, Germany; Charité—Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany; Universitätsklinikum Marburg, Klinik für Innere Medizin, Marburg, Germany; Hämatologisch-Onkologische Praxis Eppendorf (HOPE) and Universitäres Cancer Center Hamburg (UCCH), Hamburg, Germany; Universitätsklinikum Carl Gustav Carus, Medizinische Klinik I, Dresden, Germany; Ulm University Hospital, Department of Internal Medicine I, Ulm, Germany; Universitätsklinikum Jena, Klinik für Innere Medizin II, Jena, Germany; University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; Klinik und Poliklinik für Innere Medizin C, Hämatologie und Onkologie, Transplantationszentrum, Palliativmedizin, Universität Greifswald and Klinik für Hämatologie, Onkologie und Palliativmedizin-Sarkomzentrum, HELIOS Klinikum Bad Saarow, Bad Saarow, Germany; Onkologie Ravensburg, Ravensburg, Germany; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany

Background: FOLFOX plus nivolumab has become standard of care for first-line therapy of patients (pts) with advanced gastroesophageal cancer (aGEC). The efficacy of 2nd line VEGF-2 inhibition with ramucirumab (Ram) plus chemotherapy after progression to immunochemotherapy remains unclear.

Methods: Medical records of consecutive pts with aGEC enrolled in the multi-centre randomized phase II AIO-STO-0417 trial who had tumor progression after 1st line FOLFOX plus nivolumab and ipilimumab were retrospectively analysed. Pts were divided into two groups based on the subsequent 2nd line therapy: Ram plus chemotherapy (ramucirumab group) or chemotherapy alone (control group). Outcomes were compared between both groups in the overall population and in subgroup analysis according to best response (CR/PR) under 1st line therapy and tumor PD-L1 expression. Results: In total, 83 pts (38 Ram group, 45 control group) were included. The most frequent 2nd line therapy in the Ram group was Ram plus paclitaxel (85%). In the overall population, median progression-free survival (PFS) in the Ram group was longer than in the control group (4.5 vs. 2.9 months). Responders (CR/PR) to 1st line immunochemotherapy who received Ram containing 2nd line therapy (n = 15) showed a clearly prolonged median OS counted from start of 1st line therapy (28.9 vs. 16.5 months), as well as 2nd line OS (9.6 vs. 7.5 months), PFS (5.6 vs. 2.9 months) and DCR (53% vs. 29%) compared to the control group (n = 24). PD-L1 CPS ≥ 1 (status known for 77% of pts) was 42% and 44% for the Ram and the control group, respectively. Patients with CPS ≥ 1 in the Ram group (n = 16) showed a trend towards better tumor control (ORR 25% vs. 10%, DCR 44% vs. 30%) and improved survival (total OS 11.5 vs. 8.0 months; 2nd line OS 6.5 vs. 3.9 months; PFS 4.5 vs. 1.6 months) compared to the control group (n = 20). Conclusions: Ramucirumab is effective as 2nd line treatment after progression on 1st line FOLFOX plus dual checkpoint inhibition, especially in patients with initial response and positive PD-L1 expression. Sequential angiogenesis inhibition with anti-VEGFR-2 targeting therapy following immunochemotherapy might be a promising option to overcome resistance to immunotherapy, which warrants further investigations in a larger cohort. Clinical trial information: NCT03647969. Research Sponsor: Bristol-Myers Squibb; Lilly.
A phase 2 single-arm study of berzosertib in combination with irinotecan in patients with progressive TP53 mutant gastric and gastro-esophageal junction cancer.

Shannon Stockton, Heloisa P. Soares, Farshid Dayyani, Anwaar Saeed, Edward S. Kim, Ning Jin, George Hosni Yacoub, Jennifer Whisenant, G. Dan Ayers, Steven Gore, Satya (Nanu) Das, Jordan Berlin; Vanderbilt University Medical Center, Nashville, TN; Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT; University of California Irvine, Division of Hematology/Oncology, Department of Medicine, Orange, CA; University of Pittsburgh Medical Center (UPMC), Department of Medicine, Division of Hematology and Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA; City of Hope, Irvine, CA; Ohio State University Wexner Medical Center, Columbus, OH; Wake Forest University Department of General Internal Medicine, Winston-Salem, NC; National Cancer Institute, Rockville, MD; Astra Zeneca, Gaithersburg, MD

Background: TP53 mutations are reported in 30-70% of patients with metastatic/unresectable gastric (G) and gastro-esophageal junction (GEJ) adenocarcinoma and are associated with a poor prognosis. Novel therapeutics are needed. Gastrointestinal cancer cell lines with TP53 mutations demonstrate reliance on the ataxia telangiectasia and Rad3-related protein kinase (ATR) axis for DNA damage repair (DDR) in vitro. The ATR axis is triggered by single-strand DNA breaks and thus combining ATR inhibitors with topoisomerase I (TopI) inhibitors may have a synergistic effect, particularly in patients with TP53 mutant tumors. Irinotecan, a TopI inhibitor, is an established cytotoxic therapy for gastric and GEJ adenocarcinoma. We evaluated irinotecan in combination with the ATR inhibitor berzosertib (formerly M6620) in patients with TP53-mutated gastric and GEJ adenocarcinoma. Methods: This was a single-arm phase II study in third-line patients with G/GEJ cancers possessing TP53 mutations (exon 2 and exons 4-11). Patients received irinotecan 180 mg/m^2 IV and berzosertib 270 mg/m^2 IV on days 1 and 15 every 28 days. The primary endpoint was overall response rate (ORR) (Ha: 35% and Ho:15%). A subset of patients underwent biopsies on C1D1 post-irinotecan and C2D2 to evaluate the expression of DDR biomarkers Y-H2AX, KAP1 p-Ser 824, and p-ATR. Results: A total of 17 patients were enrolled. Of 16 efficacy-evaluable patients, one experienced a partial response. The ORR was 6.2% thus the primary endpoint was not met. The disease control rate was 56.2%. Median progression-free survival was 4.01 months [95% CI 2.07-Not Reached]. Median overall survival was 6.21 months [95% CI 4.83-8.61]. No new safety signals were observed with the experimental treatment combination and the most common ≥ grade 3/4 treatment-related adverse events were neutropenia (4/17, 23.5% patients), anemia (3/17, 17.6%), febrile neutropenia (2/17, 11.8%), and diarrhea (2/17, 11.8%). No grade 5 events occurred. Conclusions: Although the primary endpoint of ORR was not met, the combination of irinotecan and berzosertib in patients with TP53-mutated G/GEJ adenocarcinoma was well-tolerated and demonstrated anti-tumor activity comparable to other agents with published later-line data (e.g. ramucirumab+paclitaxel, TAS-102). Analyses of pharmacodynamic biomarkers of DNA damage repair are in process. While further clinical development of berzosertib is not planned, other ATR inhibitors are being explored in combination with irinotecan in gastrointestinal malignancies, including G/GEJ cancer. Clinical trial information: NCT03641313. Research Sponsor: U.S. National Institutes of Health.
FLOT plus nivolumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: Results from the randomized phase 2 IKF-S628/AIO-STO-0417 (Moonlight) trial of the AIO.

Sylvie Lorenzen, Thorsten Oliver Goetze, Ralf Dieter Hofheinz, Peter C. Thuss-Patience, Tobias Nicolaas Dechow, Jorge Riera-Knorrenschild, Gunter Schuch, Kim Barbara Luley, Christine Koch, Eray Goekkurt, Harald Schmalenberg, Thomas Jens Ettrich, Udo Lindig, Daniel Pink, Michael Bitzer, Claus Bolling, Nils Homann, Sabine Junge, Claudia Pauligk, Salah-Eddin Al-Batran; Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany and Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt, Germany; Universitätasmédizin Mannheim, Tagestherapiezentrum am ITM, Mannheim, Germany; Charité–Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany; Onkologie Ravensburg, Ravensburg, Germany; Universitätasmédizin Marburg, Klinik für Innere Medizin, Marburg, Germany; Hämato logic-Onkologische Praxis Altona (HOPA), Hamburg, Germany; University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; Universitätasmédiklinikum der Goethe-Universität, Medizinische Klinik 1, Frankfurt Am Main, Germany; Hematology Oncology Practice Eppendorf (HOPE) and University Cancer Center Hamburg (UCCH), Hamburg, Germany; Städtisches Klinikum Dresden, IV. Medical Clinic, Dresden, Germany; Ulm University Hospital, Department of Internal Medicine I, Ulm, Germany; Universitäts klinikum Jena, Klinik für Innere Medizin II, Jena, Germany; Klinik und Poliklinik für Innere Medizin C, Hämatologie und Onkologie, Transplantationszentrum, Palliativmedizin, Universität Greifswald and Klinik für Hämatologie, Onkologie und Palliativmedizin-Sarkomzentrum, HELIOS Klinikum Bad Saarow, Bad Saarow, Germany; Universitätsklinikum Tübingen, Medizinische Klinik I, Tuebingen, Germany; Agaplesion Markus Krankenhaus, Hämatologie/Onkologie, Frankfurt, Germany; Klinikum Wolfsburg, Med. Klinik II, Wolfsburg, Germany; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany; Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany

Background: FOLFOX plus nivolumab (nivo) has become standard of care for first-line therapy of patients (pts) with esophagogastric adenocarcinomas. FLOT is a well-established standard of care triplet regime. Some physicians may consider a triplet in patients with aggressive disease. The aim of this Arm C part of the Moonlight trial was to evaluate the safety and efficacy of the combination of FLOT plus nivo. Methods: Moonlight is a multi-cohort phase-II trial. The results for Arm C evaluating FLOT + nivo (240 mg) q2w as first-line therapy in all-comers are presented here. Primary endpoint was progression-free survival at 6 months (PFS@6), main secondary endpoints were safety, OS, and overall response rate (ORR). Results: Fifty-two patients were enrolled. Baseline characteristics were: median age 61y, GEJ 65%. Sixty-five percent had centrally assessed PD-L1 CPS ≥1 (available in 96% of pts). Pts. received a median number of 8 cycles of FLOT and nivo and 42% received further line treatment. FLOT plus nivo was well tolerated and feasible with the most frequent adverse events of grade 3 being decreased neutrophils (40.4%), anemia (5.8%) and thromboembolic events (7.7%). After a median follow-up of 9.4 months, 3- and 6-month progression-free survival rates were 85% and 42%, respectively. Median PFS was 6.6 months and median OS 10.8 months. ORR and disease control rate (DCR) were 54% and 87%, respectively. Compared to the pooled study cohorts A and A1 (n = 90 pts) utilizing mFOLFOX plus nivo and ipilimumab (non-randomized comparison), FLOT plus nivo was associated with greater DCR (87% vs. 78%) and 3-months PFS (85% vs. 72%). Conclusions: FLOT and nivo is feasible and seems to be associated with improved disease control in the early course of therapy. FLOT plus nivo may represent an option for select patients with aggressive, rapidly progressive disease. Clinical trial information: NCT03647969. Research Sponsor: Bristol-Myers Squibb.

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Osemimatamab in combination with capecitabine and oxaliplatin (CAPOX) as a first line treatment of advanced G/GEJ cancer: Updated data of cohort C from a phase I/IIa, multicenter study (TranStar102/TST001-1002).

Lin Shen, Dan Liu, Ning Li, Weijian Guo, Tianshu Liu, Hongli Li, Jiayi Li, Yuxian Bai, Yanhong Deng, Zhi-xiang Zhuang, Meili Sun, Qingxia Fan, Fuyou Zhao, Liang Han, Zhenzhong Xia, Jianming Wang, Charlie Qi, Li Xu, Xueming Qian, Caroline Germa; Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, Haidian District, China; Beijing Cancer Hospital, Beijing, China; Henan Cancer Hospital, Zhengzhou, China; Department of Gastrointestinal Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Gastrointestinal Medical Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin’s Clinical Research Center for Cancer, Tianjin, China; Xiamen Key Laboratory of Antitumor Drug Transformation Research, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical Univers, Shamen, China; Department of Gastroenterology, Harbin Medical University Cancer Hospital, Harbin, China; Sixth Affiliated Hospital of Sun Yat-Sen University, Guangdong, China; Department of Oncology, The Second Affiliated Hospital of Soochow University, Suzhou, China; Central Hospital Affiliated to Shandong First Medical University, Jinan, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; The First Affiliated Hospital, Bengbu Medical College, Bengbu, China; Xuzhou Central Hospital, Xuzhou, China; Suzhou Transcenda Therapeutics Co., Ltd., Guangzhou, China; Transcenda Holding, San Diego, CA; Suzhou Transcenda Therapeutics Co., Ltd, Suzhou, China; XEXUS Global Biopharma Clinical Development Consulting, LLC, Phoenixville, PA; Suzhou Transcenda Therapeutics Co., Ltd, Suzhou, Jiangsu, China; Transcenda Therapeutics, Princeton, NJ

Background: Adding a claudin18.2 antibody to a chemotherapy is a clinically validated approach for patients with high CLDN18.2 expressing tumors. TST001 is a best in class differentiated antibody whose improved CLDN18.2 affinity and enhanced antibody-dependent cellular cytotoxicity, leads to anti-tumor activity in low to medium CLDN18.2 expressors gastric cancer cells. Pre-clinical studies also showed that TST001 has stronger tumor regression effects than the IMAB362-analog at the same dose. Methods: The efficacy and safety of osemimatamab with CAPOX as 1st line treatment with G/GEJ cancer was explored in a dose escalation and expansion phase 1/2 study in China (Cohort C, NCT04495296). Positive claudin18.2 expression (membranous staining $1+ intensity in $10% of tumor cells) as assessed centrally using the LDT assay was required in the expansion phase only.

Results: As of Dec 31, 2022, 64 patients were dosed with osemimatamab in combination with CAPOX, 15 patients received osemimatamab at doses ranging from 1 to 8 mg/kg Q3W in the dose escalation and 49 patients at 6 mg/kg in the dose expansion. The median follow up was 151 days. Patient characteristics were typical of 1st line G/GEJ cancer, with relatively higher percentage of peritoneal disease (48.4%). Nausea (65.4%), vomiting (46.2%) and hypoalbuminemia (65.4%) were the most common adverse events related to TST001 at dose of 6mg/kg in 52 patients (3 patients in dose escalation and 49 patients in dose expansion), most of them were grade 1 or 2 (only one patient experienced grade 3 nausea and vomiting, and one experienced grade 3 hypoalbuminemia). In the expansion cohort, 40 of the 45 patients with measurable lesions had at least one post-treatment tumor assessment. 27 achieved partial response (PR) of which 21 were confirmed. There was no obvious trend in improved efficacy with higher level of CLDN18.2 expression based on overall response rate (ORR). Progression free survival (PFS) and duration of response (DOR) were still immature.

Conclusions: TST001 in combination with CAPOX as first-line treatment for the patients with G/GEJ cancer is safe and encouraging anti-tumor activities have been observed regardless of the CLDN18.2 expression levels above 1+ intensity in $=10% tumor cells per central LDT assay. Updated ORR, mPFS and mDOR will be presented at the time of the congress. Clinical trial information: NCT04495296. Research Sponsor: Suzhou Transcenda Therapeutics Co., Ltd.
Heterogeneous baseline immune cell infiltration landscape as a predictor of pathological complete response in locally advanced esophageal squamous cell carcinoma (ESCC) following neoadjuvant chemotherapy and immunotherapy: Results from a single-arm, phase II clinical trial (SEEK-01).

Guangyu Yao, Renfeng Wang, Zhenliang Huang, Chaoxiang Du, Borong Chen, Zhenyang Lin, Tao Zhang, Zhonghua Wu, Hong Fan; Zhongshan Hospital, Fudan University, Shanghai, China; Zhongshan Hospital, Fudan University (Xiamen Branch), Xiamen, China

Background: Neoadjuvant immunotherapy and chemotherapy have shown promise in improving outcomes for patients with locally advanced ESCC, but the response to treatment can vary among patients. Therefore, there is a need to identify predictive biomarkers that can guide treatment decisions and improve patient outcomes. The infiltration of immune cells within the tumor microenvironment has been shown to be an important factor in cancer progression and response to treatment. In this study, we sought to explore the immune microenvironment prospectively related to treatment response of Neoadjuvant immunotherapy by scRNAseq.

Methods: This was a single-arm phase II clinical trial, planned to enroll 20 locally advanced ESCC patients (cT2-4N0-1M0). After neoadjuvant chemotherapy (paclitaxel-albumin + carboplatin) combined with tislelizumab, patients received minimal invasive esophagectomy (MIE). Prior to neoadjuvant therapy, fresh tumor tissues were obtained via endoscopy and used for scRNAseq analysis, to evaluate the predictive capacity of the immune microenvironment. Pathological outcomes were assessed and divided into pCR, MPR defined as >10% residual tumor excluding pCR, and non-MPR defined as ≤10%. Results: Out of 18 enrolled patients, 15 completed neoadjuvant therapy and MIE surgery since March 2022. Of these 15 patients, 3 achieved pCR, 2 got MPR, and 10 were non-MPR, with a total of 51,208 single cells sequenced. Both groups showed similarly low expression of PD-L1 (5.7% vs. 2.3%). Comparing pCR to non-MPR patients, the former showed a significant increase in T lymphocytes (CD8+(17.1% vs.1.1%), Regulatory T(20.2% vs.4.0%)), plasma cell(22.0% vs.8.3%), and mature dendritic cell(1.5% vs.0.5%); a significant decrease in B cells(0.9% vs. 1.9%), neutrophils(1.7% vs.11.0%), and tumor cell, as well as a similar expression of macrophage(5.6% vs.6.6%) and monocyte, indicating a clear difference in the immune cell infiltration landscape between two groups. Furthermore, we identified a new subtype of plasma cell which was highly enriched in the non-MPR group, even though the pCR group showed a great increase in plasma cells in total. Conclusions: This study demonstrates the heterogeneity of baseline immune cell infiltration landscape in Locally Advanced ESCC, in which pCR and non-MPR patients exhibited entirely different profiles, and provide a potential predictor of response to neoadjuvant immunotherapy. Our findings suggest that baseline immune cell infiltration status, rather than pd-L1 expression, could accurately predict pCR or non-MPR before treatment, which could guide personalizing and minimize the need for trial-and-error approaches. Research Sponsor: None.
Camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced esophageal squamous cell carcinoma (ESCC): A single-arm, phase II trial.

Lei Gong, Yueyang Yang, Hongdian Zhang, Yufeng Qiao, Haitong Wang, Peng Ren, Peng Tang; Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin, China

**Background:** This study (NCT05476380) aimed to evaluate the safety and efficacy of neoadjuvant camrelizumab plus chemotherapy in patients with locally advanced ESCC, and to explore the potential risk factors of tumor immune microenvironment (TIM) which affect the efficiency of immunotherapy.

**Methods:** Patients with resectable locally advanced thoracic ESCC, staged as T1b-4a, N2-3 (>3 stations), and M0 or M1 lymph node metastasis (confined to supraclavicular lymph nodes) were enrolled. Eligible patients received intravenous camrelizumab (200 mg, day 2) plus paclitaxel (175 mg/m², day 1) and cisplatin (75 mg/m², day 1) for three 21-day cycles before surgery. The primary endpoint was major pathological response (MPR), defined as ≤10% residual viable tumor cells in resected tissue. In order to screen out the potential biomarkers, the dissected lymph nodes were collected in the pathological complete response (pCR) and non-pCR groups. The infiltrated immune cells and the status of PD-L1 was evaluated by flowcytometry.

**Results:** From February 20, 2021 to July 7, 2022, 38 patients were enrolled. 34 (89.5%) patients completed the full three-cycle treatment successfully. 34 patients underwent surgery and all received R0 resection. The MPR and pCR rates were 67.6% (23/34) and 17.6% (6/34), respectively. There were 2 (5.9%) patients having complete response of the primary tumor but residual disease in lymph nodes alone (ypT0N+). 32 (94.1%) patients had any-grade treatment-related adverse events, with the most common being leukocytopenia (73.5%). 18 (52.9%) patients had adverse events of grade 3 or worse. No treatment-related deaths occurred. Based on our findings, positive lymph nodes were one of the important reasons that the patients could not achieved pCR. TIM of the lymph nodes were then tested. Compared with MPR group, the infiltrated lymphocyte cells in the non-MPR group decreased from 93% to 52.4% (p = 0.02), the infiltrated CD8⁺ T cells also decreased from 11.8% to 5.9% (p = 0.02). However, the CD4⁺ T cells showed no significant difference between the MPR and non-MPR groups (46.2% vs 55%, p = 0.27). The expression of PD-L1 in the immune cells is one of the biomarkers for checkpoint inhibitors. In this trial, the expression of PD-L1 in the CD8⁺ T cells showed significant difference between the MPR and non-MPR groups (14.5% vs 6.7%, p = 0.02). Myeloid-derived suppressor cells (MDSCs) are a group of vastly heterogeneous immunosuppressive cells derived from immature myeloid progenitors that have been linked to poor patient prognosis and immunosuppression. We found more infiltrations of MDSCs in the non-MPR group compared with the MPR group (9.7% vs 4.7%, p = 0.04). **Conclusions:** Neoadjuvant camrelizumab combined with chemotherapy shows promising efficacy and good safety in ESCC patients. Poor response to immunotherapy was related to lymph node metastasis in the TIM. Clinical trial information: NCT05476380. Research Sponsor: Hengrui Medicine.
Effectiveness and safety of camrelizumab in advanced esophageal cancer: A prospective multicenter observational cohort studies (ESCORT-RWS).

Zhihao Lu, Jun Zhao, Zhe Yang, Na Li, Junsheng Wang, Shuanghu Yuan, Yusheng Wang, Suyi Li, Fengming Ran, Yinghua Ji, Yanqiao Zhang, Chen Wang, Lixin Wan, Ming Wang, Liang Liang, Xiaofang Dai, Guanghui Cheng, Wei Li, Peng Zhen, Lin Shen; Peking University Cancer Hospital, Beijing, China; Changzhi People’s Hospital Affiliated to Changzhi Medical College, Changzhi, China; Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China; The First Affiliated Hospital of Shihezi University School of Medicine, Xinjiang, China; Anyang Tumor Hospital, Anyang, China; Shandong Cancer Hospital and Institute, Jinan, China; Affiliated Cancer Hospital of Shanxi Medical University, Taiyuan, China; Anhui Provincial Cancer Hospital, Hefei, China; Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China; Harbin Medical University Cancer Hospital, Harbin, China; Ganzhou People’s Hospital, Ganzhou, China; Nanyang Central Hospital, Nanyang, China; Ganzhou Central Hospital, Ganzhou, China; Sichuan Province Hospital, Chengdu, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; China-Japan Union Hospital of Jilin University, Changchun, China; The First Hospital of Jilin University, Changchun, China; Chifeng Cancer Hospital, Chifeng, China

Background: Camrelizumab, an anti-programmed death 1 (PD-1) monoclonal antibody, has demonstrated survival benefits in patients with advanced or metastatic esophageal squamous cell carcinoma. However, the real-world effectiveness and safety of camrelizumab in patients with advanced esophageal cancer are largely unknown. Methods: In this prospective multicenter observational cohort study (NCT04616040), patients with advanced esophageal cancer who were scheduled to receive camrelizumab at the discretion of the physicians in charge were screened for inclusion. Clinical outcomes were treatment emergent adverse events (TEAEs), objective response rate (ORR), disease control rate (DCR), time to treatment discontinuation (TTD), progression free survival (PFS), and overall survival (OS). Results: Between Dec. 24, 2020 and Dec. 30, 2022, data were available for 624 patients (median age: 64.5 years; 74 [11.9%] aged ≥75 years; 515 [82.5%] men; 20 [3.2%] ECOG PS ≥2; 602 [96.5%] esophageal squamous cell carcinoma) from 42 institutions in China. All patients received at least one dose of camrelizumab-containing therapy, including 305 (48.9%) in the first-line, 238 (38.1%) in the second-line, and 81 (13.0%) in the third or later line settings. Most patients were treated with camrelizumab plus chemotherapy (487 [78.0%], primarily taxane and platinum-based chemotherapy in 284 [45.5%] patients), followed by camrelizumab plus antiangiogenic therapy (64 [10.3%]), camrelizumab monotherapy (46 [7.4%]), and camrelizumab plus antiangiogenic therapy and chemotherapy (27 [4.3%]). TEAEs occurred in 541 (86.7%) patients, most commonly anemia (41.2%), decreased white blood cell (38.5%), and decreased neutrophil count (28.5%). No new safety signals were noted. At the data cutoff (Dec. 30, 2022), 152 (24.4%) patients were still on treatment. Median follow-up estimated by the reverse Kaplan-Meier method and effectiveness outcomes are summarized in the Table. Conclusions: The real-world effectiveness and safety profiles of camrelizumab in advanced esophageal cancer patients are generally consistent with those observed in pivotal clinical trials. Research Sponsor: None.
Modified FOLFOX plus/minus nivolumab and ipilimumab vs FLOT plus nivolumab in patients with previously untreated advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction: The randomized phase 2 IKF-S628 Moonlight trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO).

Sylvie Lorenzen, Thorsten Oliver Goetze, Peter C. Thuss-Patience, Jorge Riera-Knorrenschild, Eray Goekkurt, Tobias Nicolaas Dechow, Thomas Jens Ettrich, Ralf Dieter Hofheinz, Kim Barbara Luley, Daniel Pink, Udo Lindig, Gunnar Folprecht, Gunter Schuch, Michael Bitzer, Volker Heinemann, Stefan Angermeier, Claus Bolling, Sabine Junge, Claudia Pauligk, Salah-Eddin Al-Batran; Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, and Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt, Germany; Charité–Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany; Universitätsklinikum Marburg, Klinik für Innere Medizin, Marburg, Germany; Hämatologisch-Onkologische Praxis Eppendorf (HOPE) and Universitäres Cancer Center Hamburg (UCHC), Hamburg, Germany; Onkologie Ravensburg, Ravensburg, Germany; Ulm University Hospital, Department of Internal Medicine I, Ulm, Germany; Universitätsmedizin Mannheim, Tagestherapiezentrum am ITM, Mannheim, Germany; University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; Klinik und Poliklinik für Innere Medizin C, Hämatoologie und Onkologie, Transplantationszentrum, Palliativmedizin, Universität Greifswald and Klinik für Hämatologie, Onkologie und Palliativmedizin-Sarkomzentrum, HELIOS Klinikum Bad Saarow, Bad Saarow, Germany; Universitätsklinikum Jena, Klinik für Innere Medizin II, Jena, Germany; Universitätsklinikum Carl Gustav Carus, Medizinische Klinik I, Dresden, Germany; Hämatologisch-Onkologische Praxis Altona (HOPA), Hamburg, Germany; Universitätsklinikum Tübingen, Medizinische Klinik I, Tübingen, Germany; Klinik der Universität München-Großhadern, Medizinische Klinik III, München, Germany; Klinikum Ludwigsburg, Klinik für Innere Medizin, Gastroenterologie, Hämato-Onkologie, Pneumologie, Diabetologie und Infektioologie, Ludwigsburg, Germany; Agaplesion Markus Krankenhaus, Hämato/Onkologie, Frankfurt, Germany; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany

Background: FOLFOX plus nivolumab has become standard of care for first-line therapy of patients (pts) with esophagogastric adenocarcinomas (EGA). The AIO-STO-0417 trial (Moonlight) is a multi-cohort treatment optimization trial that evaluates the combination of FOLFOX alone (Arm B) vs FOLFOX plus nivolumab (nivo) and ipilimumab (ipi) administered in parallel (Arm A/A1) or sequentially (Arm A2) and FLOT plus nivolumab administered in parallel (Arm C) for 1L-treatment of metastatic or advanced inoperable Her-2 negative EGA. The aim is to generate signals whether a. dual checkpoint inhibition or b. a triplet chemotherapy is beneficial in the context of nivolumab therapy for this disease. Methods: Pts were randomized 1:1 to Arm A (mFOLFOX q2w plus nivo 240 mg q2w + ipi 1 mg/kg q6w administered in parallel) or B (mFOLFOX alone). In a subsequent phase pts were randomized 1:2 to Arm A1 (identical to Arm A) or A2 (three cycles of mFOLFOX followed by nivo q2w + ipi q6w, with optional repetition). In a final phase, all pts were allocated to single Arm C (FLOT q2w + nivo q2w). The primary endpoint was progression-free survival (PFS) based on the ITT population for Arm A vs Arm B and PFS rate at 6 months (PFS@6) for Arms A2 and C. Main secondary endpoints were PFS and ORR. Here, we present results for Arms A/A1, A2 and B. Results: A total of 262 pts were enrolled, Arm A (n=60), Arm B (n=60), Arm A1 (n=30), Arm A2 (n=60) and Arm C (n=52, results presented elsewhere). Baseline characteristics were comparable in all arms. Overall PD-L1 expression (CPS ≥1) was low with 41% and balanced between Arms A/A1, A2 and B. Analysis of pooled Arms A/A1 (n=90) showed an increase in toxicity (pts with AEs grade ≥3 88% vs 65% in Arm B and 75% in Arm A2, treatment related SAEs grade ≥3 A/A1 41% vs B 18% vs A2 17%) but not in activity. Arm A/A1 compared with Arm A2 was more effective in terms of PFS@6 (48% vs 30%), median PFS 5.8 vs 4.0 months and objective response rate (ORR) 46% vs 30%. Conclusions: Albeit the small number of pts in each cohort we conclude that in the first-line setting of metastatic EGA. a) Chemo plus dual checkpoint inhibition administered in parallel is associated with an increase in toxicity but not activity. b) Although associated with lower toxicity the use of sequential chemo followed by IO monotherapy is insufficient. The relatively low numbers of patients with PD-L1 CPS ≥1 may have impacted these results. Clinical trial information: NCT03647969. Research Sponsor: Bristol-Myers Squibb.
Advancing individualized care in advanced gastroesophageal cancers (GEC): A quality improvement initiative.

Matthew Strickland, Bethany Delcuze, Ilona Dewald, Kelly E. McKinnon, Jeffrey D. Carter, Cherilyn Heggen; Massachusetts General Hospital, Boston, MA; PRIME Education LLC, Fort Lauderdale, FL

Background: Biomarkers have become increasingly important in the treatment of metastatic gastroesophageal cancers (mGEC) with new targeted and immune-based therapies relying on biomarkers to identify patients who may benefit from these therapies. Here, we aimed to identify real-world challenges mGEC care teams face in implementing biomarker testing and evidence-based treatment choices. Methods: In July–September 2022, 74 health care professionals (HCPs) who treat mGEC at 3 US community oncology clinics completed surveys assessing practice patterns, challenges, and confidence related to treating mGEC. HCPs (N = 24) participated in interdisciplinary audit and feedback (AF) sessions to examine clinical evidence and develop clinic-specific action plans to address identified gaps. Results: Participating practices reported that ~22% of their practice is dedicated to GEC care. Participants represented the interprofessional GEC care team: medical oncologists (27%), radiation oncologists (1%), surgeons (1%), advanced practice professionals (32%), nurse/nurse navigators (32%), and other HCPs (5%). Providers reported testing for HER2, EGFR, FGFR, NTRK, microsatellite instability, tumor mutational burden, and PD-L1 in ~55-65% of advanced GEC patients. Most providers reported HER2 testing at time of diagnosis (91%) with 18% reporting testing at time of clinical or radiologic progression and 24% when new metastases are detected. Top reported barriers to use of predictive biomarker testing were long turnaround times for tests (32%) and keeping up to-date with current testing recommendations (23%). Top reported challenges in selecting therapies for GEC were keeping up with clinical evidence (35%) and delayed, pending, or unavailable biomarkers at the time of treatment selection (20%). Clinic action plans focused on specific gaps including (1) improved HCP education on guideline-concordant biomarker use (2) improving testing turnaround times, and (3) improving referrals to clinical trials based on biomarker results. The educational intervention increased correct identification of guideline concordant treatment for stage IV esophageal cancer (48% pre- and 72% post-AF) and confidence in use of biomarkers for treatment decision-making for patients with GEC (high/very high in 46% pre- and 72% post-AF). Conclusions: While molecular testing is becoming increasingly critical for mGEC care, HCPs report challenges with testing workflows and difficulty keeping up with developments in clinical data and guidelines. Clinic-specific interventions to improve biomarker workflows and ongoing educational initiatives to keep HCPs informed of the latest evidence-based best practices in biomarkers and associated therapies can address these gaps to improve outcomes for patients with GEC. Research Sponsor: Supported by an educational grant from Merck Sharp & Dohme Corp.
Phase II study of telomelysin (OBP-301) in combination with pembrolizumab in gastro-esophageal (GEA) adenocarcinoma.

Manish A. Shah, Jennifer Rachel Eads, Sandipto Sarkar, Sahrish Khan, Reem Sharaiha, David Carr-Locke, Lillian Chang, Gregory Ginsberg, Lisa DiCicco, Luis Garcia-Marcano, Erika Hissong, Doron Betel; NYP, Weill Cornell, New York, NY; University of Pennsylvania, Philadelphia, PA; Weill Cornell Medicine, New York, NY; Weill Cornell Medical College, New York, NY; University of Pennsylvania Health System, Philadelphia, PA; New York Presbyterian-Weill Cornell Medicine, New York, NY; Weill Cornell Medical College, New York-Presbyterian Hospital, New York, NY

Background: OBP-301 is a novel, replication-selective adenoviral construct that incorporates the human telomerase reverse transcriptase gene (hTERT) promoter, which is highly expressed in tumors but not in normal, differentiated adult cells, to regulate expression of the early adenoviral genes, E1A and E1B. OBP-301 has been evaluated as a single agent, and demonstrated immune responses and clinical activity in phase I studies. We examined OBP-301 in combination with pembrolizumab in a multicenter phase II study as a novel mechanism to improve immunotherapy in advanced gastric cancer.

Methods: Eligible patients had advanced GEA that had progressed on at least 2 lines of prior therapy for incurable, advanced disease. Patients were required to have adequate end-organ function, measurable disease by RECIST 1.1, and a PD-L1 CPS > 1. Patients received OBP-301 at 2x10^{12} viral particles via direct tumor injection every two weeks x 4 injections as well as pembrolizumab 200 mg IV every 3 weeks. The primary endpoint was objective response rate (ORR). The null hypothesis that the ORR is 15% was tested against the Ha ORR 30%. We used a Simon two-stage design, requiring 3 or more responses in 18 patients in the first stage to proceed to stage two. The study was closed after successfully completing stage one of the Simon’s two stage design to formally examine OBP-301 + pembrolizumab in an immunotherapy (IO) refractory GEA population. Tissue was collected for single cell RNA Sequencing to examine the tumor immune microenvironment pre- and post-OBP-301 injections.

Results: From May 2019 to Oct 2022, we enrolled 16 patients, median age 65 (range 43-81), male n = 13. OBP-301 direct tumor injection was well tolerated, median OBP-301 injections 3 (range 1-5). Toxicity attributed to OBP-301 included grade 2 fatigue/weakness (25%), grade 2 fever (18.7%), and a single incidence each of grade 2 nausea, anemia, grade 3 melena, and grade 4 diabetes mellitus (6.25%). We observed 3 patients (19%) with a partial response (PR), thereby meeting the Simon two-stage threshold. The responses were durable; two patients with PR are currently without evidence of disease (one completed 2 years of pembrolizumab, one underwent resection of primary tumor after 15 months), and the 3rd patient is now in month 12 of treatment. Further, one patient with brain metastases demonstrated regression of metastatic disease following progression on immunotherapy alone. All patients were mismatch repair proficient.

Conclusions: OBP-301 viral particle injection into the tumor is feasible and safe. OBP-301 with pembrolizumab has encouraging activity in GEA, with durable responses and demonstration of activity in immunotherapy refractory disease. Single Cell RNA Sequencing data of the pre- and post-injection immune effects of OBP-301 will be presented. A formal phase II study of OBP-301 + pembrolizumab in IO refractory GEA patients is underway.

Circulating tumor DNA and association with CAR-T cell therapy response in gastric and pancreatic cancer patients.

Sindhu Kubendran, Julia L. Boland, Adham A Jurdi, Audrey Ween, Gabriel Baker, Hong Ma, Raffaele Baffa, Zonghai Li, Gregory P. Botta; Department of Medicine, University of California San Diego, La Jolla, CA; Department of Medicine, George Washington University Hospital, Washington, DC; Natera Inc., Austin, TX; Division of Hematology Oncology, Department of Medicine, University of California San Diego Moores Cancer Center, San Diego, CA; Division of Hematology Oncology, Department of Medicine, University of California San Diego Moores Cancer Center, La Jolla, CA; CARsgen Therapeutics, Inc, Houston, TX; CARsgen Therapeutics, Inc, Houston

Background: Circulating tumor DNA (ctDNA) is a form of cell free DNA that can be used to detect and measure cancer molecular residual disease (MRD) before and after systemic therapy. There are no data pertaining to the assessment of MRD in patients with solid tumors treated with chimeric antigen receptor T-cell (CAR-T) therapy. Here, we evaluated a tumor-informed ctDNA assay in the setting of gastric and pancreatic malignancies treated with claudin18.2 (CT041)-targeted CAR-T cell therapy (NCT04404595). Methods: A single-center review between 7/1/2021 – 1/1/2023 identified 10 patients with pancreatic or gastric carcinoma who received CAR-T CT041 cell therapy. Eight patients were ctDNA positive prior to treatment and had blood samples serially drawn before and after CAR-T cell therapy. Banked plasma was analyzed for ctDNA using a tumor-informed Signatera, mPCR-NGS ctDNA assay (Natera, Inc.). The correlative prognostic value of ctDNA to predict response after CAR-T cell therapy was analyzed by RECIST 1.1 criteria. Results: Pre- and post-treatment serial ctDNA was available for 8 of 10 (3/5 gastric and 5/5 pancreatic cancer) patients and all 8 were ctDNA positive prior to CAR-T CT041 cell therapy. The median nadir of ctDNA was on day 14 after CT041 infusion. Of the 8 patients with detectable ctDNA, 5 (62.5%) became undetectable at some time after CT041 therapy, while 3 (37.5%) remained ctDNA positive throughout treatment. The disease control rate (DCR) was 80% for anytime negative ctDNA patients (4/5). Of patients with responsive disease after CT041 CAR-T, 2/3 (67%) achieved undetectable ctDNA and 1/3 (33%) had a ctDNA reduction by 95%. Both patients with stable disease developed undetectable ctDNA. In those patients with progressive disease, 1/3 (33%) had a negative anytime ctDNA. One patient with a complete response had undetectable ctDNA and target lesion response, then later developed progressive disease detectable by ctDNA 3 months prior to radiography. Overall survival was higher (9.1 months vs. 3.7 months) in those who achieved anytime undetectable ctDNA. Conclusions: Tumor-informed ctDNA correlates with response to CAR-T cell therapy in gastrointestinal malignancies. Ongoing clinical trials of CT041 CAR-T cell therapy will continue ctDNA analysis prospectively. Characteristics of initially ctDNA positive patients receiving CAR-T therapy. Clinical trial information: NCT04404595. Research Sponsor: Carsgen Inc.; Natera Inc.

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<th>Anytime cDNA (-) (N=5)</th>
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Adjuvant nab-paclitaxel plus S-1 versus capecitabine plus oxaliplatin for patients with stage III gastric adenocarcinoma after D2 dissection: A multicenter, open-label, randomized phase 3 study.

Yu Pengfei, Yan Du, Zhiyuan Xu, Litao Yang, Jieer Ying, Ping Chen, Yunhai Wei, Yingjie Wu, Xiaojing Zhang, Zhilong Yan, Zhiheng Chen, Hongtao Xu, Yong Li, Zhichao Zheng, Nong Xu, Xiangdong Cheng; Zhejiang Cancer Hospital (University of Chinese Academy of Sciences Cancer Hospital), Hangzhou, China; Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hangzhou, China; Ningbo Second Hospital, Ningbo, China; Huzhou Central Hospital (Zhejiang University Huzhou Hospital), Huzhou, China; Affiliated People’s Hospital of Ningbo University, Ningbo, China; The No.1 people’s hospital of Huzhou (The directly affiliated hospital of Huzhou Teachers College), Huzhou, China; Ningbo First Hospital, Ningbo, China; The First Hospital of Jiaxing, Jiaxing, China; Lishui Central Hospital, Lishui, China; First Affiliated Hospital of Nanchang University, Nanchang, China; Liaoning Cancer Hospital & Institute, Shenyang, China; The First Affiliated Hospital of Zhejiang University, Hangzhou, China

Background: Multiple clinical studies have shown that adjuvant chemotherapy could prolong the survival of patients after radical resection, it is necessary to explore better treatment options for patients with stage III gastric adenocarcinoma (GAC). We designed this study to evaluate the efficacy and safety of adjuvant nab-paclitaxel combined with S-1 (AS) versus capecitabine combined with oxaliplatin (CAPOX) in GAC.

Methods: Patients with stage III GAC after D2 radical resection and achieved R0 resection were randomized 1:1 to receive adjuvant AS (nab-paclitaxel: 100 mg/m², d1 and 8, q3w; S-1: 40-60 mg, bid, d1-14, q3w) or CAPOX (oxaliplatin: 130 mg/m², d1, q3w; capecitabine: 1000 mg/m², bid, d1-14, q3w) for 8 cycles. Stratification analysis was performed according to histological type (differentiated vs undifferentiated GAC) and AJCC 8th pathological staging (IIIa vs IIIB and IIIC). The primary endpoint was 3-year disease-free survival (DFS) rate, secondary endpoints were overall survival (OS) and safety.

Results: Between March 20, 2020 and January 17, 2023, 313 patients were randomized to receive AS (n = 156) or CAPOX (n = 157). Baseline characteristics were generally balanced between the two groups. Median follow-up time was 5.16 months. The 1-year DFS rates were 87.14% and 70.16%, in the AS and CAPOX groups, respectively. The median DFS and 3-year DFS rates were not reached. The 1-year OS rate was 88.47% in AS group, and 63.89% in CAPOX group. At date cutoff, 12 patients (peritoneal recurrence, 1 patient; locoregional recurrence, 3 patients; distant recurrence, 8 patients) relapsed in the AS group and 16 patients (peritoneal recurrence, 4 patients; locoregional recurrence, 5 patients; distant recurrence, 8 patients; tumor marker recurrence, 1 patient) relapsed in the CAPOX group; some patients had multiple recurrence sites. 2 patients (1 patient for GAC; 1 patient for other diseases) died in the AS group and 11 patients (9 patients for GAC; 2 patients for other diseases) died in the CAPOX group. The median relative dose intensity of nab-paclitaxel was 90.32%, of S-1 was 80.77%, of oxaliplatin was 77.44% and of capecitabine was 78.55%. The incidence of adverse events (AEs) of any grade and grade 3/4 were 79.49% and 39.74% in the AS group, 72.61% and 22.93% in the CAPOX group. In the AS and CAPOX groups, neutropenia (31.63% vs 20.13%), leukopenia (29.71% vs 17.25%), anemia (27.80% vs 23.00%) and thrombocytopenia (4.15% vs 17.25%) were the most common AEs.

Conclusions: Compared with CAPOX regimen, AS regimen has better survival rates and acceptable tolerability. AS provided new potential adjuvant regimen for stage III gastric cancer after D2 resection. Clinical trial information: NCT04135781. Research Sponsor: CSPC ouyi Pharmaceutical Group Co., Ltd.
Perioperative immunochemotherapy (mDCF + avelumab) in locally advanced gastro-esophageal adenocarcinoma: A phase II trial.

Thierry Alcindor, Pierre-Olivier Fiset, Touhid Opu, Mehrnoush Dehghani, Nicholas Bertos, Carmen L. Mueller, Jonathan Cools-Lartigue, Marc Hickeson, Victoria Marcus, Sophie Camilleri-Broêt, Alan Spatz, Gertruda Evaristo, Mina Farag, Giovanni Artho, Arielle Elkrief, Ramy Saleh, Veena Sangwan, Lorenzo Ferri; McGill University Health Center, Montréal, QC, Canada; McGill University, Montréal, QC, Canada; Research Institute of McGill University Health Centre, Montreal, QC, Canada; McGill University Health Centre, Montreal, QC, Canada; Research Institute of the McGill University Health Centre, Montreal, QC, Canada; McGill University, Montreal, QC, Canada; Division of Thoracic and Upper GI Surgery, McGill University, Montreal, QC, Canada; McGill University Health Centre, Montréal, QC, Canada; Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; RI-MUHC, Montreal, QC, Canada

Background: Perioperative chemotherapy improves cure rate in locally advanced gastro-esophageal adenocarcinoma (GEA). Immune checkpoint inhibitors have activity in GEA. This trial is testing the hypothesis that the addition of avelumab, an anti-PD-L1 antibody, to perioperative mDCF chemotherapy, will increase the pathologic complete response (pCR) rate, a potential surrogate for overall survival, in comparison with a historical pCR rate of 7%.

Methods: Single-arm phase II study (NCT03288350) of avelumab + chemotherapy (modified docetaxel/cisplatin/5-FU or mDCF) given every 2 weeks x 4 cycles before and after surgery. Planned sample size of 50 operated patients. The hypothesis cannot be refuted if ≥6 patients show pCR, the primary endpoint. Inclusion criteria: histologically proven GEA, locally advanced disease (cT3-4 and/or N+), adequate organ function, WHO performance status 0-1. Exclusion criteria: other histology, metastatic stage, use of immunosuppressants, serious autoimmune disease, intake >10 mg prednisone/d. Adverse effects prospectively recorded per NCI CTCAE guidelines. Pathological response and tumor regression grade (TRG) determined by CAP criteria: 0=complete; 1=near complete; 2=moderate; 3 = poor/no response. Data presented as median (range), KM determined survival.

Results: Study accrual completed August 2022: 51 patients enrolled, 45 M/6 F, age 64 (18-79), ECOG 0 (35) and 1 (16). One patient withdrew consent after 2 treatment cycles and is excluded from efficacy analysis. Tumor anatomic site: Esophagus =19(38%)/gastroesophageal junction 21(42%)/subcardia stomach 10(20%). Staging: cT3 (88%), cT4 (6%), N+ (62%). Histology: all adenocarcinoma; dMMR 9/50 in 18%; CPS, 1, 1-5, 6-10, >10 in 0%/33%/27%/40% of tumors tested. All 4 pre-operative cycles administered to 48/50 (96%); 36/50 received ≥2 adjuvant treatment cycles and 46/50 received all 8 cycles. Grade 3-4 toxicity events from neoadjuvant therapy affected: GI tract (diarrhea 4%); respiratory system (pneumonia 4%); endocrine system (adrenal insufficiency 2%). Other common side effects (grades 1-2, incidence >15%) were: fatigue, diarrhea, skin rash/pruritus. Post-operative mortality at 30 and 90 days was 0/50 (0%) and 1/50 (2%). R0 resection was achieved in 48/50 (96%); a median of 36 (13-78) lymph nodes were resected. Pathological response was TRG 0/1/2/3 in 7/2/16/25 with pCR seen in 7 (14%), meeting the primary endpoint. Major pathologic response (TRG 0 and 1) was seen in 9 (18%), but without correlation with CPS or dMMR biomarker status. At 37.5 (9-71) months follow up, overall survival at 1, 2, and 3 years is 93.6%, 75.7%, and 69.2%. MPR showed a trend to improved survival (p = 0.06).

Conclusions: The neoadjuvant combination of avelumab with chemotherapy (mDCF) shows promising safety and efficacy in gastroesophageal adenocarcinoma, without obvious correlation to known biomarkers. Clinical trial information: NCT03288350. Research Sponsor: EMD Serono as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.; MUHC Foundation.
Predicting role of circulating tumor DNA and blood-based tumor mutational burden in esophageal squamous cell carcinoma receiving chemoradiotherapy combined with toripalimab: Exploratory analyses from a phase II trial (EC-CRT-001).

BaoQing Chen, Shi-Liang Liu, Qiaoqiao Li, Mengzhong Liu, Hong Yang, Mian Xi; Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: EC-CRT-001 is a phase II trial investigating the efficacy of toripalimab (an anti-PD1 antibody) combined with definitive chemoradiotherapy (CRT) in locally advanced esophageal squamous cell carcinoma (ESCC) and the results demonstrated encouraging antitumor activity and acceptable toxicity. This exploratory analysis was performed to evaluate the role of circulating tumor DNA (ctDNA) and blood-based tumor mutational burden (bTMB) for efficacy prediction. Methods: Forty-two patients from the phase II trial (NCT04005170) who received toripalimab (240 mg every 3 weeks for up to 1 year, or disease progression, or unacceptable toxicity) combined with definitive CRT (irradiation with 50.4 Gy in 28 fractions concurrent with 5 cycles of weekly paclitaxel in 50 mg/m² and cisplatin in 25 mg/m²) were enrolled. Plasma samples were collected before, during, and after CRT. Targeted next-generation sequencing was performed on a total of 118 plasma samples and 35 matched tumor samples using a panel covering 474 cancer-associated genes. Results: Twenty-six (62%) of 42 patients achieved clinical complete response (cCR) at three months after CRT. ctDNA was detected in 29 (72.5%) of 40 patients at baseline. The positive rate of ctDNA decreased to 43.9% (20/41) during CRT and continued to descend to 27.0% (10/37) at the completion of CRT. A higher cCR rate was observed in patients with negative during-CRT ctDNA compared to those with detectable ctDNA (82.6% vs. 38.9%, P = 0.008). Patients with post-CRT detectable ctDNA also had poorer cCR rate (30.0% vs. 77.8%, P = 0.017). Within a median follow-up of 24.0 months (IQR 13.7-27.9), the median progression-free survival (PFS) was 12.2 months (95%CI: 8.4-16.0) and median overall survival (OS) was not reached for the whole cohort. Patients with during-CRT detectable ctDNA had shorter PFS compared to ctDNA-negative patients (HR = 2.57, 95%CI: 1.18-5.60, P = 0.014). Similarly, patients with post-CRT detectable ctDNA also had a significantly increased risk of disease progression (HR = 2.88, 95%CI: 1.21-6.83, P = 0.012) and death (HR = 3.67, 95%CI: 1.41-9.55, P = 0.004). Moreover, patients with higher bTMB (> 1) detected during CRT were associated with a favorable OS (HR = 0.33, 95%CI: 0.13-0.88, P = 0.027). Improved PFS was also observed in those patients with higher post-CRT bTMB (> 3) (HR = 0.28, 95%CI: 0.08-0.96, P = 0.042). Conclusions: Negative ctDNA status and higher bTMB during or after CRT were associated with better tumor response and favorable survival in ESCC patients who underwent definitive CRT combined with toripalimab. Dynamic ctDNA has great potential in predicting efficacy and risk of disease progression in ESCC. Clinical trial information: NCT04005170. Research Sponsor: Guangdong Esophageal Cancer Institute (Q202109).
Integration of trastuzumab (T), with or without pertuzumab (P), into perioperative chemotherapy (CT) of HER-2 positive gastric (GC) and esophagogastric junction cancer (EGJC): First results of the EORTC 1203 INNOVATION study, in collaboration with the Korean Cancer Study Group, and the Dutch Upper GI Cancer group.

Anna Dorothea Wagner, Heike I. Grabusch, Murielle Mauer, Uberto Fumagalli Romario, Yoon-Koo Kang, Olivier Bouche, Sylvie Lorenzen, Markus H. Moehler, Peter C. Thuss-Patience, Anneli Elme, Gunnar Folprecht, Uwe Marc Martens, Denis Michel Smith, Maria del Carmen Galan Guzman, Michel Pierre Ducreux, Marc Diez Garcia, Guillaume Piessen, Sun Young Rha, Maïke Collilienne, Florian Lordick; Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; Grow School for Oncology and Reproduction, Maastricht University Medical Center, Maastricht, Netherlands; European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium; European Institute of Oncology - IRCCS, Milan, Italy; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South); Robert Debré University Hospital, Reims, France; Technical University of Munich, School of Medicine, Department of Internal Medicine, Munich, Germany; University Hospital, Johannes Gutenberg University, Mainz, Germany; Charité University Medicine Berlin, Department of Haematology, Oncology and Cancer Immunology, Campus Virchow-Klinikum, Berlin, Germany; North Estonia Medical Centre, Tallinn, Estonia; Universitätsklinikum Carl Gustav Carus, Medizinische Klinik I, Dresden, Germany; SLK-Clinics Heilbronn, Heilbronn, Germany; CHU de Bordeaux - Group Hospitalier Sud - Hopital Haut-Leveque, Pessac, France; ICO L’Hospitalet - Hospital Duran i Reynals (Institut Catala D’Oncologia), Barcelona, Spain; Université Paris Saclay, Villejuif, France; Vall d’Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; University of Lille, Department of Digestive and Oncological Surgery, Claude Huriez University Hospital, Lille, France; Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea, Republic of (South); University Cancer Center Leipzig (UCCL), Leipzig, Germany

Background: 10-20% of GC are HER-2 positive. The role of perioperative anti-HER2-directed treatment is yet undefined. Methods: This randomized, open-label phase II-trial investigates the benefit of combining T alone or with P and perioperative CT for GC and EGJC. Between 2015 and 2021, 172 of a planned 215 patients (pts) with centrally confirmed, positive HER-2 status and resectable GC or EGJC (UICC TNM stages Ib-III) were included. Recruitment was prematurely terminated due to slow accrual. Pts were randomized in a 1:2:2 ratio to: Arm A (CT alone) (35 pts); Arm B (CT + T [8mg/kg, followed by 6mg every 3 weeks]) (67 pts); Arm C (CT + T + P [840mg every 3 weeks]) (70 pts). CT was initially cisplatin (80 mg/m² d1) and capecitabine (2 x 1000 mg/m²/d d1) for 3 cycles before and after surgery. After publication of the FLOT-4 study, the protocol was amended. CT changed to four cycles FLOT (Al-Batran Lancet 2019) with FOLFOX or CAPOX as alternative for pts ineligible for FLOT. In the experimental arms, T and P were continued beyond CT at the same dose for a total of 17 cycles. Major pathological response rate (mpRR) determined by central pathology review was the primary endpoint. The study was designed to have 80% power to detect an increase in mpRR from 25% with CT to 45% with CT+T+P or CT+T with a one-sided alpha of 10%. CT+T+P was first tested versus CT and if positive, CT+T would be tested versus CT. Results: Out of 172 pts randomized, 161 fulfilled all important eligibility criteria and started their allocated treatment (per protocol population). 62.1% of pts had EGJC and 72.0% an intestinal subtype. Main CT regimens were cisplatin+capecitabine (42.2%) and FLOT (46.6%). In Arm A:B:C, 90.9%, 92.2% and 81.3% completed neoadjuvant treatment. Major reason for treatment discontinuation was toxicity (70%). Surgery was performed in 84.8%, 98.4%, 92.2% pts in Arm A:B:C. R0 resection rates were 83.9%, 90.3% and 85.9%. At present, results of central pathology review of mpRR are available for 126 out of 150 operated pts (84.0%). Pts not operated (n=11) were considered as failures for mpRR. MpRR was 23.3%, 37.0%, 26.4% in Arm A:B:C. The increase of 3.1% (80% CI: [-9.5%, 15.7%], one-sided p=0.378) in Arm C vs. A was not statistically significant. The increase in Arm B vs. A was 13.7% (80% CI: [0.7%, 26.7%], one-sided p=0.099). MpRR was 33.3%, 53.3% and 37.9% in Arm A:B:C after amending the protocol while, in contrast, it was 8.3%, 16.7% and 12.5% before. Conclusions: The primary endpoint analysis did not meet the pre-specified criteria of efficacy for the combination of CT+T+P. However, CT+T showed interesting response rates, especially with FLOT as CT backbone. Follow-up data including survival is necessary to define the clinical value of this regimen. Clinical trial information: NCT02205047. Research Sponsor: This study was funded by an unrestricted educational grant from Roche to EORTC.
Concordance among the three commercially available PD-L1 assays for esophageal squamous cell carcinoma.

Lizhen Wang, Jhe-Cyuan Guo, Chien Huai Chuang, Grace Cao, Stacey Huang, Jia Liu, Tony Guo, Tsung-Che Wu, Shuang Li, Jing Lin, Hsi-Yu King, Jun Cai, Wenjun Yang, Qingyuan Liu, Simon Allen, Yifan Wang, Jingyu Zhang, Chih-Hung Hsu; Roche (China) Holding Ltd., Shanghai, China; National Taiwan University Cancer Center, Taipei, Taiwan; National Taiwan University Biomedical Park Hospital, Hsinchu, Taiwan; Genentech, South San Francisco, CA; Roche, Shanghai, China; National Taiwan University Hospital, Taipei, Taiwan

Background: Immune checkpoint inhibitors are now standard-of-care for patients with esophageal squamous cell carcinoma (ESCC). The predictive significance of PD-L1 expression in ESCC has been investigated by different antibodies, scoring algorithms and cutoff values in several phase III trials. However, it remains controversial whether PD-L1 is a predictive biomarker for response to PD-1/PD-L1 blockade. Evaluating the concordance of the commercially available PD-L1 assays is essential to understand the discrepancy in the ESCC clinical trials, and helpful to further investigate the predictive value of PD-L1 expression.

Methods: 145 archival tumor samples were obtained from 131 patients with ESCC (stage I-IV) at National Taiwan University Hospital. Formalin-fixed, paraffin-embedded archival tumor samples were assessed by three commercially available PD-L1 assays: VENTANA SP263, Dako 22C3 and Dako 28-8 assays. Assays were performed in a College of American Pathologists accredited central laboratory and scored for PD-L1 staining by using multiple metrics including tumor cell score (TC), immune cell score (IC) and combined positive score (CPS) or tumor area percentage (TAP). Analytical concordance was calculated pairwise between assays using the Spearman ($\rho$) rank correlation coefficient. Classification concordance, including agreement between clinically relevant scoring algorithms, was investigated using positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA) at multiple cutoff values to assess the overlap between populations by using different assays.

Results: SP263, 22C3 and 28-8 assays showed good analytical correlation for TC staining (Spearman’s rank correlation coefficient 0.8–0.9). Correlation was lower for IC (Spearman’s rank correlation coefficient 0.59-0.61). There was moderate overlap between populations identified by SP263 and 28-8 or 22C3 based on CPS or TAP algorithm at multiple cutoff values. OPAs for these 3 assays ranged from 68%–88% at various matched algorithms. The SP263 and 22C3 PD-L1 assays appeared relatively more sensitive, assigning a higher proportion of patients as PD-L1 positive or high, compared to 28-8 assay. When using assay-specific clinically relevant algorithm, moderate classification agreement was seen for SP263 versus 22C3 or 28-8. Differences were observed between patient populations with tumor classified as PD-L1 high versus PD-L1 low/negative using CPS$\geq$10, TAP$\geq$10% and TC$\geq$1%. The PPA between 22C3 CPS$\geq$10 and SP263 TAP$\geq$10 or 28-8 CPS$\geq$10 or 28-8 TC$\geq$1% were 75%, 57% and 68% respectively.

Conclusions: This study is the first dataset to compare various PD-L1 assays in ESCC. Differences in classification of patients with PD-L1 high versus low/negative using clinically relevant algorithms suggest that caution should be taken when comparing data across the trials. Research Sponsor: Roche.
Multi-dimensional cell-free DNA-based liquid biopsy and early detection of gastric cancer.

Yu Pengfei, Min Wu, Guangyu Ding, Hua Bao, Yian Du, Zhiyuan Xu, Litao Yang, Jingquan Fang, Xingmao Huang, Qian Lai, Jia Wei, Junrong Yan, Shanshan Yang, Peng He, Haimeng Tang, Xue Wu, Yang Shao, Dan Su, Xiangdong Cheng; Department of Gastric Surgery, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang, China; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, Jiangsu, China; Department of Pathology, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang, China; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China

Background: Gastric cancer is one of the most common cancer types. Most patients were diagnosed at advanced stages and experienced poor prognosis. A non-invasive assay for the detection of early-stage gastric cancer is highly desirable for reducing the gastric cancer-associated mortality. Methods: We prospectively collected a study cohort of 249 participants including 110 pathologically confirmed with stage I-II gastric cancer and 139 with non-cancerous conditions. A plasma sample was collected from each patient before conventional screening modalities for gastric cancer. We performed whole-genome sequencing with plasma samples and profiled four types of cell-free DNA (cfDNA) characteristics, fragment size pattern, copy number variation, nucleosome coverage pattern, and single nucleotide substitution. We used these differential profiles to develop an ensemble model to identify gastric cancer patients from non-cancer individuals. We further collected a validation cohort consisting of 73 gastric cancer patients and 94 non-cancer individuals to validate the cfDNA-based assay. Additionally, we compared the performance of our assay and conventional gastroscopy in a hypothetical 100,000 screening population by Monte Carlo simulation. Results: The liquid biopsy assay that incorporated four types of cfDNA characteristics was able to identify early-stage gastric cancer patients from non-cancer individuals at an AUROC of 0.962 in the study cohort and 0.972 in the validation cohort. At a specificity of 92.1% (128/139), it achieved a sensitivity of 88.2% (97/110) in the study cohort. With this threshold, in the validation cohort, 91.5% (86/94) of healthy individuals and 91.8% (67/73) of gastric cancer patients were correctly identified. In both study and validation cohorts, the inferred probabilities of cancer showed consistent trends to increase with pathological stages in the cancer group and disease statuses in the non-cancer group. Of note, our approach detected all gastric tumors located in the cardia and fundus (100.0%, 19/19), which could be challenging for gastroscopic examination. Additionally, through in-silico simulations, we showed that our cfDNA-based non-invasive assay may detect 96.3% more gastric cancer cases than conventional gastroscopy owing to higher sensitivity and anticipated better participant compliance in a large hypothetical screening population. Conclusions: We introduced a liquid biopsy assay using multiple dimensions of cfDNA characteristics that could accurately identify early-stage gastric cancer from non-cancerous conditions. As a cost-effective non-invasive approach, it may provide population-wide benefits for the early detection of gastric cancer. Research Sponsor: None.
Induction chemotherapy plus definitive chemoradiotherapy versus chemoradiotherapy alone in esophageal squamous cell carcinoma: Long-term results and exploratory analyses of a randomized controlled trial.

Mian Xi, BaoQing Chen, Shi-Liang Liu, Yujia Zhu, Lei Zhao, Mengzhong Liu; Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China

Background: The previous results of our trial demonstrated that the addition of induction chemotherapy (IC) prior to definitive chemoradiotherapy (CRT) failed to significantly improve response rate or 3-year survival in patients with locally advanced esophageal squamous cell carcinoma (ESCC). Here, we report the long-term results and exploratory analyses to further evaluate the therapeutic value of IC in ESCC.

Methods: This was a single-institution, open-label, randomized, phase II trial. Patients with previously untreated, unresectable, stage II–IVA ESCC were randomly assigned in a 1:1 ratio to receive induction docetaxel (75 mg/m² on day 1) and cisplatin (75 mg/m² on day 1) every 3 weeks for two cycles, followed by concurrent CRT, or CRT alone. The primary endpoint was overall response rate at 3 months after CRT. Second endpoints were overall survival (OS) and progression-free survival (PFS). The relationship between tumor response to IC and long-term survival was analyzed as an exploratory, post-hoc analysis. Moreover, baseline tumor biopsies were evaluated by RNA-seq to identify patients who are more likely to benefit from IC.

Results: Between May 2015 and September 2017, 110 eligible patients were randomly assigned to the IC+CRT group (n=55) or the CRT group (n=55). The overall response rate was 74.5% in the IC+CRT group versus 61.8% in the CRT group (P=0.15). At a median follow-up of 74.9 months, the 5-year OS rate was 31.8% in the IC+CRT group and 29.1% in the CRT group (P=0.68; HR, 0.91; 95% CI, 0.58–1.43). Similarly, no significant differences were identified in 5-year PFS between groups (30.5% vs. 25.5%, P=0.51; HR, 0.86; 95% CI, 0.56 to 1.34). Patients who responded to IC had significantly better survival than nonresponders. Six key genes were identified based on RNA-seq and gene expression comparison between responders and nonresponders after IC. Risk-score model was constructed by these key genes and then validated.

Conclusions: Addition of induction docetaxel plus cisplatin before definitive CRT still failed to provide an obvious survival benefit in ESCC based on long-term follow-up. However, this strategy did result in a significantly improved survival in IC responders. Our results also revealed potential molecular biomarkers to predict who may benefit from IC. Clinical trial information: NCT02403531. Research Sponsor: None.
Pembrolizumab, radiotherapy, and chemotherapy in neoadjuvant treatment of malignant esophago-gastric diseases (PROCEED): Assessment of pathologic response and toxicity in a prospective, phase II single-arm trial.

Pooja Karukonda, Brian G. Czito, Eileen Duffy, Hope Elizabeth Uronis, Thomas A. D’Amico, John H Strickler, Donna Niedzwiecki, Christopher Willett, Manisha Palta; Duke Cancer Institute, Durham, NC; Duke University Medical Center, Durham, NC; Division of Medical Oncology, Duke University School of Medicine, Durham, NC; Duke University, Durham, NC

Background: A standard treatment paradigm for locally advanced, resectable, non-metastatic esophageal or gastric adenocarcinomas (EGA) is neoadjuvant chemoradiation (CRT) followed by surgery. Historical pathologic complete response (pCR) rates after CRT with carboplatin/paclitaxel in the CROSS trial are low at 23%. Efficacy of adjuvant immunotherapy has since been shown in this patient population. The main objectives of this trial were to investigate whether neoadjuvant CRT + pembrolizumab improves pCR compared to the historical control of CRT alone, and also determine the associated acute and post-surgical toxicity of this approach. Methods: Single-institution, prospective phase II trial (NCT03064490) evaluating the efficacy and safety of neoadjuvant pembrolizumab + CRT followed by adjuvant pembrolizumab in patients with locally advanced operable EGA. CRT (45 Gy/25 fractions with concurrent weekly carboplatin [AUC 2] and paclitaxel [50 mg/m² of BSA]) with 3 cycles of pembrolizumab was administered as neoadjuvant therapy. Patients also received 3 cycles of adjuvant pembrolizumab after surgical resection if they did not experience Grade 3 (G3) toxicity during neoadjuvant treatment. Baseline characteristics were collected. Pathologic response was scored from 0-3 per tumor regression grading. The percentage of patients with pCR (score of 0) are described. Acute toxicities are defined per CTCAE v4 and include relevant events occurring within 90 days after treatment. Results: Accrual is complete, with 35 patients with cT2-3N0-2M0 EGA enrolled from 10/10/2017-10/07/2022. 28/32 patients have completed neoadjuvant therapy and surgical resection. 89% of enrolled patients are male, and 94% are white. 97% have an esophageal primary, and 97% underwent R0 resection. 10/28 (35.7%; 95% CI: 17%, 53%) patients achieved a pCR. 22/32 patients have experienced treatment-related G3 non-hematologic toxicity to date (94.2% G3, 5.8% G4). 18 patients experienced ≥G3 toxicity related to neoadjuvant therapy, with 53 events overall, the majority being GI (24.5%) or metabolic/nutritional disorders (24.5%). 10 patients experienced ≥G3 toxicity related to surgery, with 16 events overall, the majority being procedural complications (31.3%) and infectious disorders (31.3%). Conclusions: Patients undergoing neoadjuvant CRT + pembrolizumab for EGA experienced higher rates of pCR and acceptable rates of treatment-related toxicity compared to historical controls. This phase II trial demonstrates the safety and efficacy of this treatment paradigm, which warrants assessment in future prospective studies. Clinical trial information: NCT03064490. Research Sponsor: Merck.
Development of an artificial intelligence algorithm for adjuvant chemotherapy based on a nationwide registry of patients with gastric cancer by the Japanese Gastric Cancer Association (JGCA).

Yasuhide Yamada, Ami Kamada, Yoshinori Kabeya, Sumito Yoshida, Hitoshi Harada, Naoki Urakawa, Shingo Kanaji, Yuma Nakamura, Kengo Nagashima, Hiroya Takeuchi, Yuichiro Doki, Yuko Kitagawa, Yasuhiro Kodera, Yoshihiro Kakeji; National Center for Global Health and Medicine, Tokyo, Japan; Healthcare & Life Sciences Services, IBM Japan, Ltd., Tokyo, Japan; Japan Medical Association Research Institute, Tokyo, Japan; Kobe University, Kobe, Japan; Biostatistics Unit, Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan; Hamamatsu University School of Medicine, Hamamatsu, Japan; Osaka University Graduate School of Medicine, Osaka, Japan; Keio University School of Medicine, Tokyo, Japan; Nagoya University School of Medicine, Nagoya, Japan; Department of Surgery, Division of Gastrointestinal Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

Background: Recent marked advances in machine learning have led to expectations of the clinical application of artificial intelligence (AI) to support medical care. Methods: A survival analysis model which consisted of 31 covariates was adopted for AI algorithms using machine learning and these were constructed using clinical data sets for training. The performance of AI algorithms was evaluated in order to determine the optimal chemotherapy including surgery alone without any adjuvant chemotherapy with the highest survival rate for each patient. This involved using clinical data for verification to compare survival of an AI-recommended treatment group, for which therapy recommended by AI was actually administered, with an AI-deprecated group, for which therapy recommended by AI was not administered. Results: The clinical characteristics of 23653 patients and treatment are described in the Table from 2011 to 2018 in a nationwide registry of gastric cancer patients in Japan by the Japanese Gastric Cancer Association and were made available for this study. S-1 monotherapy was used the most frequently of all adjuvant chemotherapy in this study. We used the "restricted mean overall survival time" (RMST) of all the patients as metrics. The RMST in the AI-recommended and the AI-deprecated groups were 51.4 and 47.5 months, respectively. Patient data for the verification were matched baseline characteristics by the propensity score. This model predicted effectively overall survival after gastrectomy. The RMST of over 80 years old patients were 43.9 in the AI-recommended and 38.3 months in the AI-deprecated, respectively. This AI algorithm recommended adjuvant S-1 more frequently for patients with higher age, male, American Society of Anesthesiologists – physical status 2, Eastern Cooperative Oncology Group performance status 1, pT3/pT4, pN2/pN3, more than the upper normal limit of preoperative blood urea nitrogen, macroscopic types 2/3, differentiated adenocarcinoma, Roux-en-Y reconstruction, and Clavien-Dindo classification grade II/III. The RMST for pStage IIA/IIB/IIIA/IIIB/IIIC were 55.7/53.9/50.3/45.7/42.2 months in the AI-recommended and 55.1/50.7/43.9/36.9/32.0 months in the deprecated. This AI algorithm showed a higher survival rate in pStage III patients particularly. Conclusions: The AI algorithm could readily be integrated into clinical practice to choose adequate adjuvant chemotherapy for each patient based on each patient’s baseline data because it trained and verified the nationwide registry has good predictive performance. Research Sponsor: Cross-ministerial Strategic Innovation Promotion Program, Cabinet Office, Japan.

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Efficacy and safety of camrelizumab combined with chemotherapy versus chemotherapy alone as preoperative neoadjuvant therapy for resectable locally advanced esophageal squamous cell carcinoma: Preliminary results from a multicenter, prospective, randomized controlled study.

Renquan Zhang, De sheng Song, Wei Liu, Long Yao, An guo Chen, Wei Ge, Shao hui Hu, Jian Chen, Yun long Huang, Jun rui Xun; The First Affiliated Hospital of Anhui Medical University, Hefei, China; Fuyang Cancer Hospital, Fuyang, China; Anqing Municipal Hospital, Anqing, China

Background: Camrelizumab combined with chemotherapy has a very ideal therapeutic effect and low toxicity in the treatment of solid tumors. Camrelizumab plays an important role in the treatment of locally advanced esophageal squamous cell carcinoma. Methods: This study is a prospective, multicenter, randomized controlled study. Inclusion criteria were patients aged 18-75 years with an ECOG score of 0-1 who had not received other treatments previously and had histologically confirmed resectable locally advanced esophageal squamous cell carcinoma (clinical stages cT1-4N1-3M0 and CT3-4N0M0). Patients received camrelizumab combined with chemotherapy (albumin paclitaxel + cisplatin in chemotherapy regimen) or chemotherapy alone (albumin paclitaxel + cisplatin in chemotherapy regimen). The primary endpoints are pathological complete remission (pCR) rate and 5-year overall survival (OS). Secondary endpoints including disease-free survival rate, duration of drug treatment and adverse events and we attempt to explore the correlation between drug efficacy and PD-L1 expression. The target sample size was 400 and patients were divided into two groups according to a 1:1 ratio who were received camrelizumab plus chemotherapy and chemotherapy alone. Results: From January 2021 to October 2022, 243 patients with resectable locally advanced esophageal squamous cell carcinoma from four centers were enrolled. Of these, 205 (85.2%) were male and 38 (15.6%) were female. Median age was 65 years. Most patients (182, 74.9%) were in clinical stage III and had an ECOG score of 1 (185, 76.1%). 150 patients had completed all clinical trial cycles and the result showed that among 90 patients who received camrelizumab plus chemotherapy, 25 patients achieved pathological complete remission (pCR), 39 achieved major partial remission (MPR), 11 had stable disease and 1 had progressive disease, with a pCR rate of 27.8% and MPR rate of 43.3%. Among 60 patients who received chemotherapy alone, 6 patients achieved pCR, 13 patients achieved MPR, 19 patients had stable disease and 2 patients had progressive disease, with a pCR rate of 10.0% and MPR rate of 26.7%. The most common adverse events were reactive cutaneous capillary endothelial proliferation (72.1%), nausea (42%), and leukopenia (15.5%), all of which were in grade 1 – 2 with manageable safety. Conclusions: Preliminary results of this study showed that the overall efficacy of camrelizumab plus chemotherapy was better than that of chemotherapy alone and the drug was safe and reliable. In future work, we will continue to analyze the survival outcomes, drug safety and the relationship between drug efficacy and PD-L1 expression and other biomarkers. Clinical trial information: ChiCTR2000040330. Research Sponsor: None.
Five-year overall survival with S-1 plus docetaxel as adjuvant treatment in curatively resected pStage III gastric cancer in JACCRO GC-07.

Wataru Ichikawa, Kazuhiro Yoshida, Yasuhiro Kodera, Masato Kitazawa, Motohiro Hirao, Yasuyuki Seto, Kenji Hibi, Shinichi Kinami, Masaya Watanabe, Shigeto Makino, Mitsugu Kochi, Takeshi Sano, Yoshhiro Kakeji, Masahiro Takeuchi, Masashi Fujii; Division of Medical Oncology, Showa University Fujigaoka Hospital, Yokohama, Japan; Gifu University, Gifu, Japan; Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan; Department of Surgery, Shinshu University, Matsumoto, Japan; Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; Department of Gastrointestinal Surgery, The University of Tokyo, Tokyo, Japan; Department of Surgery, Tokai Central Hospital, Kakamigahara, Japan; Department of Gastroenterologic Surgery, Kanazawa Medical University, Kahoku-Gun, Japan; Division of Gastroenterological Surgery, Shizuoka General Hospital, Shizuoka-Shi, Japan; Department of Surgery, Nagaoka Chuo General Hospital, Nagaoka, Japan; Department of Gastroenterological Surgery, International University of Health and Welfare Ichikawa Hospital, Ichikawa, Japan; The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; Division of Gastrointestinal Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan; Graduate School of Mathematical Sciences, The University of Tokyo, Tokyo, Japan; Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan

Background: JACCRO GC-07 is a randomized controlled trial to explore postoperative S-1/docetaxel compared to S-1 alone after D2 gastrectomy for pStage III gastric cancer (GC) patients. The second interim analysis demonstrated that the significant improvement of RFS was obtained by S-1/docetaxel compared to S-1 alone. The study was terminated by the recommendation of independent data and safety monitoring committee (Yoshida K et al. J Clin Oncol 2019; 37:1296-1304). Preplanned analysis to evaluate RFS at 3 years, the primary endpoint, was also published (Kakeji Y et al. Gastric Cancer 2022; 25:186-196). We report the 5-years follow-up data from the trial. Methods: Patients with pStage III GC were randomly assigned to receive either S-1/docetaxel (S-1 80-120mg/body on days 1-14 with a 7-day rest followed by docetaxel 40mg/m² on day 1 and S-1 80-120mg/body on days 1-14 every 21 days for 6 cycles followed by S-1 80-120mg/body on days 1-28 every 42 days for 4 cycles) or S-1 (80-120mg/body on days 1-28 every 42 days for 8 cycles) after D2 gastrectomy. Blocked randomisation was performed and stratified by the stage (IIIA, IIIB, IIIC) and histological type (differentiated or undifferentiated). The primary endpoint was 3y RFS and the secondary endpoints were OS, TTF and safety. This analysis presents the final preplanned assessment of outcomes after 5 years. Results: Of 915 randomly assigned patients, 912 patients were included in the intention-to-treat (ITT) analysis. In the final analysis, 426 recurrences and 373 deaths were confirmed among the ITT population during the median follow-up period of 63.72 months (3.52-111.87). The 5y RFS of 59.8% in the S-1/docetaxel group was significantly superior to 50.6% in the S-1 group (HR 0.726, 95% CI: 0.599-0.879, p = 0.0010) and the 5y OS was 67.9% in the S-1/docetaxel group and that of S-1 group was 60.3%, respectively (HR 0.752, 95% CI: 0.613-0.922, p = 0.0059), confirming the significant improving effect on the survival of the patient. Conclusions: Adjuvant treatment with S-1 plus docetaxel should be considered for patients with pStage III gastric cancer who underwent D2 gastrectomy without neoadjuvant chemotherapy. Clinical trial information: UMIN000010337. Research Sponsor: Japan Clinical Cancer Research Organization.
Circulating tumor DNA as a marker of recurrence risk in locoregional esophagogastric cancers with pathologic complete response.

Eric Michael Lander, Brandon Huffman, Samuel J Klempner, Vasily N. Aushev, Jennifer Ferguson, Shruti Sharma, Adham A Jundi, Minetta C. Liu, Cathy Eng, Michael K. Gibson; Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN; Dana-Farber Cancer Institute, Boston, MA; Mass General Cancer Center, Boston, MA; Natera, Inc., Austin, TX; Natera, Inc, Austin, TX; Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: Following neoadjuvant therapy and definitive surgery, up to one-third of patients (pts) with gastroesophageal adenocarcinoma with a pathologic complete response (pCR; tumor regression grade 0 [TRG0]) will recur, while up to one-half of pts with a near-pCR (TRG1) experience recurrence. Our study aims to evaluate postoperative circulating tumor DNA (ctDNA) as a prognosticator of recurrence in pts with pCR or near-pCR after curative-intent neoadjuvant chemotherapy (NAC) or chemoradiation (CRT) and surgery. Methods: We retrospectively identified pts from 11 institutions with stages I-III esophagogastric cancers who completed neoadjuvant therapy and had TRG0 or TRG1 scores at the time of curative-intent surgery. Postoperative plasma samples were collected for ctDNA analysis within a 16-week molecular residual disease (MRD) window after definitive surgery and serially during follow-up from 9/19/19 to 2/21/22. MRD by ctDNA was assessed using a personalized, tumor-informed ctDNA assay (Signatera mPCR-NGS assay). The primary outcome was recurrence-free survival (RFS), measured from the date of surgery to the first documented sign of radiographic recurrence. Survival analysis was performed using the maximum likelihood bias reduction method for Cox regression. Results: We obtained 250 blood samples from 45 pts with esophageal (N=18), gastroesophageal junction (N=17), and gastric (N=10) adenocarcinomas who received either NAC or CRT. The median follow-up for this cohort was 22.8 months (range: 0.3-81.7 months). Despite pts achieving pCR (N=12) or near-pCR (N=33), ctDNA-positivity in the 16-week MRD window (N=21) correlated with higher rates of recurrence (66.7%; 2/3) compared to the absence of ctDNA (11.1%; 2/18). Detectable ctDNA was associated with a significantly shorter RFS (HR 23.0, 95% CI 2.0-268.1; p=0.012). 35 pts had ctDNA analyzed at any post-surgical time point, where the recurrence rate was 87.5% (7/8) in ctDNA-positive pts compared to 7.4% (2/27) in ctDNA-negative pts, exhibiting a further reduction in RFS (HR 44.8; 95% CI 5.4-369.7; p<0.0001). Out of 8 ctDNA-positive pts, two (25%) converted from ctDNA-positive to ctDNA-negative with subsequent treatment. Conclusions: Within the subgroup of pts with esophagogastric adenocarcinoma and favorable pathologic responses (TRG 0-1) following neoadjuvant treatment, the presence of post-operative ctDNA identified pts with elevated recurrence risk. If validated in larger cohort studies, testing for ctDNA may be a useful biomarker to select pts at risk for recurrence with potential to inform prospective clinical trials for direction of adjuvant therapy. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.
Neoadjuvant docetaxel, oxaliplatin, and s-1 plus surgery and adjuvant s-1 for resectable advanced gastric cancer: Final survival outcomes of the randomized phase 3 PRODIGY trial.

Yoon-Koo Kang, Hyung-Don Kim, Jeong Hwan Yook, Young-Kyu Park, Young-Woo Kim, Jin Young Kim, Min-Hee Ryu, Sun Young Rha, Ik-Joo Chung, In-Ho Kim, Sang Cheul Oh, Chang Hak Yoo, Seok Yun Kang, Dae Young Zang, Sunju Kim, Sung Hoon Noh; Asan Medical Center, Seoul, Korea, Republic of (South); Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South); Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of (South); National Cancer Center, Goyang-Si, Korea, Republic of (South); Keimyung University Dongsan Hospital, Daegu, Korea, Republic of (South); Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Seoul, Korea, Republic of (South); Yonsei Cancer Center, Seoul, Korea, Republic of (South); Division of Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, Seoul, Korea, Republic of (South); Korea University Guro Hospital, Seoul, Korea, Republic of (South); Department of Surgery, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Korea, Republic of, Seoul, Korea, Republic of (South); Department of Hematology-Oncology, Ajou University Hospital, Suwon-Si, Gyeonggi-Do, Korea, Republic of (South); Hallym University Sacred Heart Hospital, Anyang, Korea, Republic of (South); SANOFI, Seocho-Gu, Korea, Republic of (South); Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea, Republic of (South)

Background: The phase 3 PRODIGY study compared neoadjuvant docetaxel, oxaliplatin and S-1 (DOS) chemotherapy followed by surgery followed by adjuvant S-1 with surgery followed by adjuvant S-1 for Korean patients with resectable locally advanced gastric cancer (LAGC) (Kang et al. J Clin Oncol. 2021). The planned analysis of the primary endpoint of PRODIGY showed that the addition of neoadjuvant DOS to surgery and adjuvant S-1 improved progression-free survival (PFS). We herein report the long-term follow-up outcomes, including overall survival (OS), from this trial. Methods: Patients with histologically confirmed primary gastric or gastroesophageal junction adenocarcinoma with clinical T2-3N+ or T4Nany disease were enrolled from 18 Korean study sites. Patients were randomly assigned to D2 surgery followed by adjuvant S-1 (40–60 mg orally twice a day, days 1–28 q6w for eight cycles; SC group) or neoadjuvant DOS (docetaxel 50 mg/m², oxaliplatin 100 mg/m² intravenously day 1, S-1 40 mg/m² orally twice a day, days 1–14 q3w for three cycles) before D2 surgery, followed by adjuvant S-1 (CSC group). The primary endpoint was PFS. OS was the secondary endpoint. This analysis presents the final assessment of the outcomes after 5 years. Results: A total of 266 and 264 patients were randomly assigned to the CSC and SC arms, respectively, among which 238 and 246 patients were treated and included in the full analysis set. As of the data cut-off date (SEP-2022), the median follow-up duration of the surviving patients was 99.5 months (range, 68.6–127.7 months). As compared to SC, CSC significantly increased the OS (adjusted hazard ratio, 0.72; 95% CI, 0.54 to 0.97; stratified log-rank P=0.028) with a 5-year OS rate of 66.8% and 63.0% for the CSC and SC arms, respectively. CSC also significantly improved the PFS (adjusted hazard ratio, 0.71; 95% CI, 0.53 to 0.94; stratified log-rank P=0.019) with a 5-year PFS rate of 60.6% and 56.9% for the CSC and SC arms, respectively. Conclusions: The addition of neoadjuvant docetaxel, oxaliplatin and S-1 (DOS) chemotherapy, as part of perioperative chemotherapy, to surgery and adjuvant S-1 prolonged the OS and PFS of Asian patients with LAGC relative to patients treated with surgery and adjuvant S-1 alone. Neoadjuvant DOS chemotherapy should be considered one of the standard treatment options for patients with LAGC in Asia. Clinical trial information: NCT01515748. Research Sponsor: None.
Neoadjuvant tislelizumab combined with chemoradiotherapy for resectable locally advanced esophageal squamous cell carcinoma (ESCC): Single arm phase II study.

Peng Jin, Yong sheng Gao, Zheng Fu, Wen feng Yang, Xue Meng; Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China; Department of Pathology, Shandong Cancer Hospital and Institute, Jinan, China; Department of PET/CT Center, Shandong Cancer Hospital and Institute, Jinan, China; Department of Thoracic Surgery, Shandong Cancer Hospital and Institute, Jinan, China

Background: This study aimed to evaluate the safety and efficacy of neoadjuvant tislelizumab combined with chemoradiotherapy in patients with resectable esophageal squamous cell cancer. Methods: This is a prospective single-arm clinical trial. A total of 20 patients with newly diagnosed resectable esophageal cancer (cT1-2N+ / cT3-4aN0-3 M0) received 2 cycles of tislelizumab (200mg every 3 weeks for 2 cycles) concurrent with chemoradiotherapy (radiotherapy: 41.4Gy in 23 fractions; chemotherapy: Paclitaxel (Albumin bound) 100mg/m², and Cisplatin 75 mg/m² once every 3 weeks for 2 cycles.) Radical esophagectomy was performed within 4-6 weeks after neoadjuvant therapy. PET/CT was performed at baseline and before surgery. Primary endpoints included pathological response rate (pCR) and major pathological response rate (MPR), the secondary endpoints were disease free survival and safety. Exploratory endpoints include molecular imaging research and immune biomarker to further explore the factors affecting the efficacy of neoadjuvant therapy for esophageal cancer. Results: Twenty patients enrolled, all of whom received neoadjuvant tislelizumab combined with chemoradiotherapy. Eighteen patients underwent radical esophagectomy. One patient underwent radical chemoradiotherapy due to lymph node metastases after neoadjuvant therapy. One patient died of pneumonia before surgery. Among 18 patients who underwent surgery, R0 was 100% (18/18), 9 patients achieved pCR (50.0%), and 13 patients achieved MPR (72.2%). Most of treatment-related adverse event (TRAE) were grade 1-2, and the most common TRAE was anemia (15, 75.0%). The grade 3 TRAE included 1 leukopenia (5.0%), 1 neutropenia (5.0%), 1 liver damage (5.0%), and 1 elevated cardiac troponin T (5.0%). A significant decrease in SUVmax was observed in both pCR and no-pCR patients after treatment. Baseline SUVmax in no-pCR patients tended to be higher than pCR patients(p=0.0642). Furthermore, a significant increase in circulating CD4⁺ T cells, CD4⁺ effector memory T cells (TEM), and M1 were found after treatment. Among the patients with pCR, the CD4⁺ TEM and cDCs after treatment were higher than those in the no-pCR patients, while Tregs and M2 were lower. Conclusions: Neoadjuvant tislelizumab combined with chemoradiotherapy for locally advanced ESCC has promising efficacy and good safety. Clinical trial information: NCT05323890. Research Sponsor: National Natural Science Foundation of China (82172720).
GaEsSeer: Early detection of gastric and esophageal cancer by integrating methylation and fragmentomics signatures in cfDNA.

Yunshi Zhong, Dong-Li He, Zhi-Guo Xiong, Bin Yan, Quan-Lin Li, Zhen Feng, Pin-Xiang Lu, Qi Guo, Meng-Jiang He, Cheng-Cheng Ma, Min-Jie Xu, Yi-Ying Liu, Ke-Hui Xie, Ming-Yang Su, Yun-Zhi Zhang, Qi-Ye He, Zhi-Xi Su, Rui Liu, Jia Fan, Jian Zhou; Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Gastroenterology, Xuhui Central Hospital, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Gastrointestinal Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Clinical Laboratory, Qingpu Branch of Zhongshan Hospital, Fudan University, Shanghai, China; Department of General Surgery, Xuhui Central Hospital, Shanghai, China; Endoscopy Center, Xuhui Central Hospital, Zhongshan Hospital, Fudan University, Shanghai, China; Singlera Genomics Ltd., Shanghai, China; Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University; Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education, Shanghai, China

Background: Esophageal and gastric cancer (EC and GC) are two common cancer types that severely impact patients' health. The 5-year survival rate for EC and GC is as low as 19% and 31%, respectively. However, early detection will significantly increase the survival rate: stage-1 EC has a 5-year survival rate of 51%, while for stage-1 GC it's 69%. Invasive screening methods, such as endoscopy and biopsy, caused low compliance. Computational tomography and carcinoembryonic antigen were limited by low sensitivity. To address this problem, we developed GaEsSeer, a non-invasive targeted-sequencing-based assay that utilizes multiple methylation and fragmentomics features of cell-free DNA (cfDNA) to accurately detect EC and GC signals in blood. Methods: cfDNA was tested using the GaEsSeer panel, which was developed using in-house genome-wide sequencing data on EC and GC samples, and public datasets from databases and literature. Methylation features, which was quantified as methylation haplotypes or methylation encoding score, and fragmentomics features including copy number and end motif ratio were taken for modeling. Separate sub-models were trained utilizing each type of feature, which were eventually combined via logistic regression to establish the final predicting model. Results: A total of 1770 participants were recruited from multiple centers. This included 787 healthy individuals, 448 cancers (209 EC, 239 GC; stage I:156, II:120, III:78, and IV:58), 174 benign esophageal diseases, and 361 benign gastric diseases. For cancer detection, the methylation-only model had an AUC of 0.909 and 0.897 in training (618 total) and test sets (617 total), respectively; while the AUC of the fragmentomics-based model was 0.885 and 0.911, respectively. The combinatorial model further improved performances, which achieves an AUC of 0.940 and 0.931 in the training and test cohorts, respectively. While the specificity remained at 96.7%, GaEsSeer detected 81.1% EC and 70.3% GC cases in the test cohort. It had a sensitivity of 74.2% and 48.9% for stage-I EC and GC, respectively. GaEsSeer also has high specificities of 87.9% and 89.8% for benign esophageal and gastric diseases, respectively. Additionally, the performance of GaEsSeer was compared with known serum cancer markers such as CEA, CA19-9, and CA72-4; and the results show that it had significantly higher sensitivity than any of these serum markers (54.8% vs 6.4% when against CEA; 53.5% vs 7.1% when against CA19-9; 50% and 16.7% when against CA72-4). Conclusions: In this pilot study, we developed the blood-based GaEsSeer assay and a model for EC and GC detection with high accuracy by stacking multiple methylation- and fragmentomics-based submodules together. Further optimization and validation of GaEsSeer using larger prospective cohorts are needed to validate its potentials for clinical application. Research Sponsor: National Key Research and Development Program of China (2019YFC1315800).

Bang Wool Eom, Hong Man Yoon, Young-Woo Kim, Jae Seok Min, Ji Yeong An, Hoon Hur, Young Joon Lee, Gyu Seok Cho, Young-Kyu Park, Mi Ran Jung, Ji-Ho Park, Woo Jin Hyung, Sang-Ho Jeong, Myeong-Cherl Kook, Mira Han, Byung-Ho Nam, Keun Won Ryu; National Cancer Center, Goyang-Si, South Korea; National Cancer Center, Goyang-Si, South Korea; National Cancer Center, Goyang-Si, Korea, Republic of (South); Dongnam Institute of Radiological & Medical Sciences Cancer Center, Busan, South Korea; Samsung Medical Center, Seoul, South Korea; Ajou University School of Medicine, Suwon, South Korea; Gyeongsang National University College of Medicine, Jinju, South Korea; Soonchunhyang University Bucheon Hospital, Bucheon, South Korea; Chonnam National University Hwasun Hospital, Hwasun, Korea, Republic of (South); Chonnam National University Hwasun Hospital, Hwasun, South Korea; Gyeongsang National University, Jinju-Si, South Korea; Yonsei University College of Medicine, Seoul, South Korea; Gyeongsang National University, Changwon-Si, South Korea; National Cancer Center, Korea, Goyang, South Korea; Biometric Research Branch, Division of Cancer Epidemiology and Prevention, Research Institute and Hospital, National Cancer Center, Goyang, South Korea; Research Institute and Hospital, National Cancer Center, Goyang-Si, South Korea

Background: In the SENORITA trial, laparoscopic sentinel node navigation surgery (LSNNS) showed no significant difference in overall and disease specific survivals compared with laparoscopic standard gastrectomy (LSG). Here, we present the effect of stomach preservation surgery on QoL and nutritional outcomes, and identify risk factors affecting QoL in stomach preservation surgery. Methods: SENORITA was a prospective multicenter randomized trial. Patients diagnosed with early gastric cancer of 3 cm or less were randomly allocated (1:1) to LSNNS or LSG. The primary endpoint was 3-year disease-free survival. This analysis focuses on long-term quality of life and nutritional outcomes of patients who finally underwent stomach-preservation surgery in the LSNNS group. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and stomach module (STO22) at 3, 12, 24, and 36 months after surgery. Linear mixed model analyses were used to evaluate differences between treatment groups. This trial is registered with ClinicalTrials.gov, NCT01804998. Results: From March 2013 to March 2017, a total of 580 patients were randomly assigned in the SENROTA trial. Among them, 258 patients underwent sentinel node navigation surgery and 198 finally underwent stomach preservation surgery. QoL data was available in 194 patients and compared with those of 257 patients who underwent standard gastrectomy. The stomach-preservation group had better QoL in physical function, dyspnea, and appetite loss of C30 and dysphagia, pain, reflux symptoms, eating restriction, anxiety, taste change, body image, and total score of STO22. Regarding nutritional outcomes, body mass index, hemoglobin, protein, and albumin levels were significantly higher in the stomach-preservation group than in the gastrectomy group. In multivariate analyses, tumor location (greater curvature) was an independent favorable factor affecting global health status, reflux symptoms, eating restriction, and total score of STO22 at 3 months in the stomach-preservation group. Segmental resection was a risk factor for diarrhea and eating restriction at postoperative 3 year. Conclusions: The stomach-preservation surgery had better long-term QoL and nutritional outcomes compared with standard gastrectomy. These findings can help decision making about treatment for patients with early gastric cancer, especially or elderly or nutritionally high risk patients. Clinical trial information: NCT01804998. Research Sponsor: This research was supported by the National Cancer Center, Republic of Korea (Grant 1110550, 1410140, 1710160, 2010150).
Response to programmed cell death protein 1 antibody in patients with Epstein-Barr virus-associated biliary tract cancer.

Wen-Zhuo He, Han-Bin Lin, Gui-Fang Guo, Liang-Ping Xia; Sun Yat-sen University Cancer Center, Guangzhou, China; Chinese Academy of Sciences, Zhongshan, China

Background: Epstein-Barr virus-associated biliary tract cancer (EBVaBTC) has a distinct genomic landscape and increased infiltration of CD3+ and CD8+ T cells. However, the efficacy of immunotherapy in EBVaBTC remains largely unknown. The aim of this study is to assess the efficacy of programmed cell death protein 1 (PD-1) antibody in EBVaBTC. Methods: Consecutive patients with metastatic biliary tract cancer diagnosed at our institution from January 2017 to December 2021 were identified. In situ hybridization was performed to detect EBV. The objective response to PD-1 antibody was assessed. We also analyzed the immune microenvironment of EBVaBTC by multiplex immunofluorescence staining, and performed the proteomic characterization of EBVaBTC. Results: A total of 131 patients with BTC who received PD-1 antibody were identified, of which 9 (6.9%) had EBVaBTC. All EBVaBTC cases were intrahepatic cholangiocarcinoma. EBVaBTC was not associated with deficient mismatch repair but with lymphoepithelioma-like carcinoma and hepatitis B virus infection. Four (44.4%) patients achieved a partial response, and the remaining five (55.6%) patients had stable disease. The response lasted for at least 12 months in 8 (88.9%) patients with EBVaBTC, including 4 patients received PD-1 antibody monotherapy. Blood EBV-DNA was detectable in all 9 patients (100%) with EBVaBTC. Multiplex immunofluorescence staining revealed more abundant CD3+ and CD8+ T cells infiltration in EBVaBTC than that of mismatch repair deficient BTC. A total of 8,379 proteins were identified by proteomics. Comparison of EBVaBTC and paired normal tissue revealed 547 differentially expressed proteins. Enrichment analysis demonstrated that differentially expressed proteins in the EBVaBTC were associated with EBV infection and T cell activation. We also observed the expression of immune checkpoint other than PD-1, including LAG-3 and TIM-3. Conclusions: Identification of EBVaBTC may represent a subset of patients with promising response to immunotherapy. Research Sponsor: Natural Science Foundation of Guangdong, China.

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Transarterial chemoembolization combined with lenvatinib and camrelizumab for unresectable hepatocellular carcinoma: A prospective, single-arm, multicenter study.

Zhibo Zhang, Maolin Yan, Yufeng Chen, Xukun Wu, Lanfang Yang, Zhengyu Yin, Hao Lu, Yongyi Zeng, Hui Zhang, Jingyao Huang, Jiafei Chen, Liang Wang, Zhongwu Chen; The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; Fujian Provincial Hospital, Fuzhou, Fujian, China; Zhangzhou Hospital Affiliated to Fujian Medical University, Zhangzhou, China; Xiamen Hospital of Traditional Chinese Medicine, Xiamen, China; Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China; Fujian Cancer Hospital, Fuzhou, China; Union Hospital Affiliated to Fujian Medical University, Fuzhou, China; Putian First Hospital, Putian, China

Background: Conversion therapy for unresectable hepatocellular carcinoma (uHCC) has attracted increasing interest in recent years. In 2020 ASCO annual meeting, one abstract reported that the combination therapy of tyrosine kinase inhibitor and anti-PD-1 antibody could be a promising conversion therapy for patients with initially uHCC. This study aims to evaluate the efficacy and safety of transarterial chemoembolization (TACE) combined with lenvatinib and camrelizumab (TACE+LEN+CAM) as a conversion therapy for uHCC. Methods: This single-arm, prospective, multicenter study was conducted on patients diagnosed with HCC (with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0-1 and Child-Pugh class A) who were ineligible for surgery. Enrolled patients received camrelizumab (200 mg every 3 weeks) and lenvatinib (bodyweight $\geq 60$ kg: 12 mg/day; $< 60$ kg: 8 mg/day) after TACE treatment. Surgery was performed after treatment response was assessed to meet the criteria of resection. Patients who did not meet the criteria for surgery continued to receive triple treatment until disease progression or intolerable toxicity. Primary endpoints were objective response rate (ORR) and safety. Secondary endpoints included percentage of patients amendable to surgery, the rate of radical (R0) resection, disease control rate (DCR). This study is registered with Chinese Clinical Trial Registry (ChiCTR2100050410). Results: Between Oct 25, 2021, and Jul 20, 2022, 55 patients were enrolled and received triple therapy (TACE+LEN+CAM). Of these, 37 (67.3%) patients had portal vein tumor thrombosis. Mean tumor diameter for all patients was 112 ± 83 mm. 52 (94.6%) patients with 2 target lesions, and 3 (5.4%) patients with > 2 target lesions. As of data cutoff on Dec 20, 2022, the median follow-up was 6.7 months (IQR 5.0-9.89). According to modified RECIST criteria, tumor response in patients included complete response to treatment in 9 patients (18.0%), partial response in 27 (54.0%), stable disease in 6 (12.0%), and progressive disease in 7 (14.0%). The ORR was 72.0%, and the DCR was 84.0%. 26 patients underwent surgery after successful conversion therapy. The MPR and pCR rates in the surgery population were 69.2% and 23.1%, respectively. The conversion rate was 55.3% and the R0 resection rate was 100%. 23 (41.8%) patients had treatment-related adverse event (TRAEs) that were grade 3-5. No grade 3-5 TRAEs occurred after surgery. Conclusions: The triple therapy (TACE+LEN+CAM) significantly improved ORR and the surgical conversion rate of uHCC patients with a manageable safety. Future large-scale randomised trials are warranted. Clinical trial information: ChiCTR2100050410. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Temporal patterns of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC).

George Lau, Bruno Sangro, Oxana V. Crysler, Wattana Sukeepaisarnjaroen, Oleg Lipatov, Manabu Morimoto, Isabelle Archambeaud, Valentina Burgio, Le Thi Tuyet Phuong, Yee Chao, Jean-Marie Peron, Marie-Luise Berres, Yoo-Joung Ko, Carrie L. McCoy, Charu Gupta, Mallory Makowsky, Alejandra Negro, Ghassan K. Abou-Alfa; Humanity and Health Clinical Trial Center, Humanity and Health Medical Group, Hong Kong Special Administrative Region, China; Liver Unit and HPB Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; Department of Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand; Bashkir State Medical University, Ufa, Russian Federation; Kanagawa Cancer Center, Yokohama, Kanagawa, Japan; Hépato-Gastro-Entérologie et Assistance Nutritionnelle, Institut des Maladies de l’Appareil Digestif (IMAD), Nantes Université, CHU Nantes, Nantes, France; Department of Medical Oncology, San Raffaele Scientific Institute, Milan, Italy; People’s Hospital 115, Ho Chi Minh City, Viet Nam; Department of Oncology, Veterans General Hospital, Taipei, Taiwan; Gastro Enterologie Hepatologie, Hôpital Purpan, Toulouse, France; Clinic of Gastroenterology, Metabolic Diseases and Internal Medicine Intensive Care, University Hospital RWTH Aachen, and Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD), Aachen, Germany; St. Michael’s Hospital, Unity Health Toronto, Toronto, ON, Canada; AstraZeneca, Gaithersburg, MD; AstraZeneca, Wilmington, DE; Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Medical College, Cornell University, New York, NY

Background: In the Phase 3 HIMALAYA study (NCT03298451) in uHCC, STRIDE (Single T Regular Interval D) significantly improved overall survival versus sorafenib (S) and had manageable safety (Abou-Alfa et al. NEJM Evid 2022). STRIDE is approved for uHCC in the United States and Japan and is recommended for approval by the European Medicines Agency. In this exploratory post hoc analysis, we assessed temporal patterns of imAEs for the STRIDE regimen in HIMALAYA. Methods: Safety was assessed in participants (pts) who received ≥1 dose of STRIDE (T 300 mg [one dose] plus D 1500 mg once every 4 weeks) or S (400 mg twice daily). Treatment causality was investigator-assessed. imAEs were defined as AEs of special interest associated with drug exposure and consistent with an immune-mediated mechanism of action for which no alternate etiology was clear. Safety was summarized descriptively overall and at specific time points after the start of treatment. Results: In total, 388 (STRIDE) and 374 (S) pts were included in the safety analysis. Median (range) duration of exposure was 5.5 (0.4–41.9) months for STRIDE (D exposure in STRIDE) and 4.1 (0.1–38.6) months for S. Any grade treatment-related AEs (TRAEs) and Grade 3 or 4 TRAEs were less frequent for STRIDE (75.8% and 25.8%, respectively) versus S (84.8% and 36.9%, respectively). Any grade imAEs and max Grade 3 or 4 imAEs occurred in 35.8% and 12.6% of pts, respectively for STRIDE. Any grade imAEs of gastrointestinal disorders and skin and subcutaneous tissue disorders were most common within the first month after treatment (3.9% and 3.1%, respectively), whereas any grade imAEs of endocrine disorders were most common between >1 and ≤2 months (6.7%). Conclusions: In HIMALAYA, AEs with STRIDE were manageable and generally low grade. Any grade TRAEs and Grade 3 or 4 TRAEs were less frequent for STRIDE versus S. Although imAEs with STRIDE could occur at any time, most were observed within the first three months after treatment. These findings continue to support STRIDE for the treatment of uHCC. Clinical trial information: NCT03298451. Research Sponsor: AstraZeneca.
Landmark analysis of OS by response status in previously treated patients (pts) with advanced hepatocellular carcinoma (aHCC): Post hoc analysis of the KEYNOTE-394 study.

Zhenggang Ren, Zhendong Chen, Wei jia Fang, Shuangyan Ou, Baek-Yeol Ryoo, Zhiqiang Meng, Yuxian Bai, Xiaoming Chen, Xufeng Liu, Juxiang Xiao, Gwo Fuang Ho, Yimin Mao, Xin Wang, Ying Ji er, Chunya Hao, Hui jia Shen, Jianxin Lin, Ken Hatogai, Abby B. Siegel, Shukui Qin; Zhongshan Hospital, Fudan University, Shanghai, China; The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China; The First Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China; Hunan Cancer Hospital, Changsha, China; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Fudan University Shanghai Cancer Center, Shanghai, China; Department of Gastroenterology, Harbin Medical University Cancer Hospital, Harbin, China; Guangdong Provincial People’s Hospital and Guangdong Academy of Medical Science, Guangzhou, China; Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China; The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China; Clinical Oncology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia; Shanghai Jiaotong University School of Medicine, Renji Hospital, Shanghai, China; West China Hospital, Sichuan University, Chengdu, China; Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China; Peking University Cancer Hospital, Beijing, China; MSD China, Beijing, China; Merck & Co., Inc., Rahway, NJ; Jinling Hospital of Nanjing University of Chinese Medicine, Nanjing, China

Background: KEYNOTE-224 and KEYNOTE-240 landmark analyses showed that objective response (OR) in pembrolizumab (pembro)-treated pts was prognostic of longer OS after the landmark. Landmark analysis was performed using the KEYNOTE-394 study to determine whether response assessment before landmark is prognostic of longer OS after landmark time in pembro-treated pts. Methods: Adults with confirmed HCC, radiographic progression during or after treatment with or intolerance to sorafenib or oxaliplatin-based chemotherapy were eligible for KEYNOTE-394. Landmark analyses of OS for responders, pts with SD, and pts with other status in these analyses at 6, 12, 18, and 24 wk after randomization were performed on the pembro arm. Tumor imaging was performed every 6 wk after randomization. Responders (R) at each landmark were defined as pts with any response assessment of CR or PR before the landmark date; all other pts were defined as nonresponders (NR). SD at each landmark was defined as pts with a response assessment of SD and no better response before the landmark date. Other was defined as pts with responses of PD or a missing/not evaluable status. Response was assessed per RECIST v1.1 by blinded independent central review. HR and 95% CI for survival after the landmark are based on the Cox regression model with the Efron method for handling ties, with response status by the landmark time as a single covariate. Results: Median time from randomization to data cutoff date (June 30, 2021) was 33.8 mo (range, 18.7-48.8) for pembro. OS after landmark time was numerically longer for R vs NR, R vs pts with SD, and pts with SD vs pts with Other status. Conclusions: KEYNOTE-394 landmark analysis supports the prognostic association between OR with pembro before the landmark and OS after the landmark observed in KEYNOTE-224 and KEYNOTE-240 in previously treated pts with aHCC. Landmark analysis also suggested longer OS after the landmark for pts who achieved a better response to pembro before the landmark. Clinical trial information: NCT03062358. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
A phase 1b study of E7386, a CREB-binding protein (CBP)/β-catenin interaction inhibitor, in combination with lenvatinib in patients with advanced hepatocellular carcinoma.

Masafumi Ikeda, Naoya Kato, Shunsuke Kondo, Yoshitaka Inaba, Kazuomi Ueshima, Mitsuhito Sasaki, Hiroaki Kanzaki, Hiroshi Ida, Hiroshi Imaoka, Yasunori Minami, Shuichi Mitsunaga, Naoshi Nishida, Sadahisa Ogasawara, Kazuo Watanabe, Takatoshi Sahara, Nozomi Hayata, Shintaro Yamamuro, Takayuki Kimura, Toshiyuki Tamai, Masatoshi Kudo; National Cancer Center Hospital East, Kashiwa, Japan; Graduate School of Medicine, Chiba University, Chiba, Japan; National Cancer Center Hospital, Tokyo, Japan; Aichi Cancer Center Hospital, Nagoya, Japan; Kindai University Faculty of Medicine, Osaka, Japan; Eisai Co., Ltd., Tokyo, Japan; Eisai Co., Ltd., Ibaraki, Japan

Background: E7386, a novel oral anticancer agent, inhibits β-catenin binding to its transcriptional co-activator, CBP, thus modulating Wnt/β-catenin signaling. The objectives of the dose-escalation part in this phase 1b study were to assess safety, tolerability, pharmacokinetics (PK), biomarkers, and preliminary efficacy of E7386 combined with lenvatinib in patients with advanced hepatocellular carcinoma (HCC) or other solid tumors. Here, we present the results from the HCC subpart.

Methods: In cycle 0, E7386 was administered orally in escalating doses once daily (QD) or twice daily (BID) for 5 or 6 consecutive days. From cycle 1 day 1, E7386 QD or BID, combined with daily oral lenvatinib (8 mg in patients with body weight <60 kg or 12 mg in patients with body weight ≥60 kg), were administered on a continuous schedule in 28-day cycles in the HCC subpart. Adverse events (AEs) were graded using CTCAE v5.0. Prophylactic antiemetics were not allowed during the dose-limiting toxicities (DLT) evaluation period but were permitted after the occurrence of nausea and vomiting. Tumor response was assessed by investigators using mRECIST (Lencioni and Llovet, 2010). PK and biomarker analyses were conducted using samples collected at defined time points.

Results: As of the cutoff date (9 December 2022), 25 patients had been treated in the HCC subpart with E7386 dose ranges from 10 to 80 mg QD and from 60 to 120 mg BID. Among 3 patients in the E7386 120 mg BID cohort, grade 3 maculopapular rash (in 1 patient) and grade 5 acute kidney injury (in 1 patient) DLTs were observed. No DLTs were observed in other cohorts. The most common treatment-emergent AEs (TEAEs; any grade) across all cohorts were nausea (n=19; 76.0%), vomiting (n=15; 60.0%), constipation (n=13; 52.0%), palmar-plantar erythrodysesthesia syndrome (n=12; 48.0%), diarrhea (n=11; 44.0%), and proteinuria (n=10; 40.0%). The most common grade ≥3 TEAEs (≥5% of patients) were proteinuria (n=5; 20.0%) and aspartate aminotransferase level increased (n=2; 8.0%). Nausea and vomiting were well controlled by a 5HT3 antagonist. Among the 25 treated patients, 9 (36.0%) partial responses (PRs) were observed, including 3 PRs in 10 patients who had received lenvatinib as a prior regimen. Cmax and AUC for E7386 increased with increasing E7386 dose.

Conclusions: E7386 100 mg BID, in combination with lenvatinib (8 or 12 mg based on body weight) QD, was determined as the recommended phase 2 dose, and was deemed tolerable and manageable with antiemetic administration. The combination showed promising activity in patients with HCC, including those pretreated with lenvatinib. Clinical trial information: NCT04008797. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
Early experience with nivolumab, gemcitabine, and lenvatinib for fibrolamellar hepatocellular carcinoma.

Paul Kent, Jordan C Tasse, Erik Schadde, Tom Kato, Abhinav Humar, Oliver M Fisher, Matthew Dixon, Tom Stockwell, Albert Cornelius, Thomas Kim, Jessica Ellison; FibroFighters Foundation, River Forest, IL; Rush University Medical Center, Chicago, IL; University of Zürich, Zurich, Switzerland; NY Presbyterian, New York, NY; upmc, Pittsburgh, OH; St George Hospital, Sydney, Australia; FibroFighters.org, Temecula, CA; DeVos Children’s Hospital, Grand Rapids, MI

Background: Fibrolamellar Carcinoma (FLC) is a rare deadly form of liver cancer affecting adolescents and young adults (AYA), presenting at an advanced stage, with up to 80% relapse, and no proven systemic therapies. Effective systemic therapies could convert patients to resectable or prolong progression free survival (PFS) and overall survival. Because of reported successes with nivolumab + lenvatinib (LEN) and of Gemcitabine (GEM) + LEN, and the potential synergy of GEM with NIV through elimination of myeloid suppressor cells in the tumor microenvironment, we offered NIV+LEN+GEN (NLG) to relapsed/refractory FLC patients ineligible for clinical trials. Our objective is to describe our initial experience using NLG in high risk AYA FLC patients. Methods: We reviewed the records of all FLC patients discussed at the FibroFighters National Tumor Board who received NLG. Results: Twenty-five patients (10F,15M), median age 20 (7-56), all stage IV, received a total of 322 cycles of NLG (median 11 cycles/patient,19 neoadjuvant, 1 adjuvant, 4 both). The median number of relapses, prior systemic therapies, and surgeries were 2(0-6), 3(0-6), and 2(0-7) respectively. Most patients had failed NIV+LEN (n = 8) or GEM+LEN (n = 7) prior to starting NGL. The 17 patients with at least one evaluation had a mean follow up of 10 months (3-23) and 18 cycles (6-38) of NLG with the best response by RECIST 1.1 of CR(1), PR(6), SD(10), and PD(0), for an objective response rate (PR+CR) of 41% and disease control rate (CR+PR+SD) of 100%, and estimated best volume response median of -20% (-89%,+10%). There have not yet been any progressions. Three of the 7 who were too soon for imaging, have had resolution of ascites. The PFS and Overall Survival at 6, 9, and 12 months are: 1.0/1.0, 0.82/0.82, 0.67/0.67. Two of 17 with carcinomatosis have no evidence of disease on PET and MRI after 10 cycles. Twenty-two of 24 are continuing NGL. Nine of 16 unresectable patients became surgical candidates, of these 4 showed > 50% necrosis histologically at surgery. 13 of 17 showed necrosis on imaging. Eleven of 16 are currently in their longest PFS since diagnosis. Sixteen patients had serial tumor-informed circulating DNA (Signatera) during therapy: Five became negative (0.0 mean tumor molecules/ml plasma), and overall mean drop was -27% (-93%, +111%). No patients have stopped therapy. The most common toxicities were hypertension and fatigue in 25% and 20% respectively, grade 1 or 2. There have been no grade 3 or 4 toxicities to date. Conclusions: Our retrospective experience with NLG for FLC offers another potential systemic option for patients who are not surgical candidates or with multiple relapses. NLG was well tolerated and provided excellent disease control to patients with few options. Prospective trials are needed. Research Sponsor: None.
An open-label, multicenter, adaptive, phase Ib/II study of QL1706 or QL1604 plus bevacizumab as first-line treatment in patients with advanced hepatocellular carcinoma.

Feng Bi, Yan-qiao Zhang, Shanzhi Gu, Yabing Guo, Zhongyuan Xu, Hao Ying, Mingxu Da, Chaoying Liu, Yaozhen Pan, Yao Huang, Zhiyu Chen, Zheng Wang, Jianbing Wu, Shangeng Weng, Yanjun Wang, Jun Zhao, Xiaokui Yu, Hui Li, Shilin Xue, Xiaoyan Kang; Department of Abdominal Oncology, West China Hospital of Sichuan University, Chengdu, China; Department of Gastroenterology Second Ward, Harbin Medical University Cancer Hospital, Harbin, China; Department of Intervention, Hunan Cancer Hospital, Changsha, China; Liver Tumor Center, Nanfang Hospital Southern Medical University, Guangzhou, China; Phase I Clinical Research Room, Nanfang Hospital Southern Medical University, Guangzhou, China; Hepatology Department of integrated Chinese and Western Medicine, Ningbo Huamei Hospital, University of Chinese Academy of Sciences, Ningbo, China; Oncology Surgery, Gansu Provincial Hospital, Lanzhou, China; Oncology Department, Wuxi People’s Hospital, Wuxi, China; Hepatology Surgery, The Affiliated Hospital of Guizhou Medical University, Guiyang, China; Hepatology Surgery, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China; Hepatology Surgery, The Southwest Hospital of AWU, Chongqing, China; Medical Oncology, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi, China; The Second Affiliated Hospital of Nanchang University, Nanchang, China; Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; Medical Oncology, The Second Hospital of Liaocheng Affiliated to Shandong First Medical University, Liaocheng, China; Department of Oncology, Changzhi People’s Hospital, Changzhi, China; Department of Medicine, Qilu Pharmaceutical Co., Ltd., Jinan, China; Statistics and Statistical Programming, Qilu Pharmaceutical Co., Ltd., Jinan, China; Medicine Department, Qilu Pharmaceutical Co., Ltd., Jinan, China

Background: Cancer immunotherapy has expanded the treatment options for advanced HCC (aHCC). Atezolizumab plus bevacizumab is approved as the standard of care for patients (pts) with aHCC. QL1706 is a novel dual immune checkpoint blockade containing a mixture of anti-PD-1 IgG4 and anti-CTLA4 IgG1 antibodies (Abs). QL1604 is a humanized mAb against PD-1. The anti-PD-1 Ab of QL1706 has the same protein sequence and was produced by using the same single clone selection method with QL1604. Here we report the safety and efficacy results from a Ph Ib/II study of QL1706 or QL1604 plus bevacizumab (beva) as first-line treatment in pts with aHCC. Methods: Eligible pts had histologically or clinically confirmed HCC; had BCLC stage B/C disease and Child-Pugh class A and B liver function; were systemic therapy naive; and were not suitable for radical surgery and/or locoregional therapy, or progressed after surgery and/or locoregional therapy. This study included 3 parts. Part 1 included a safety run-in phase and an expansion phase. Patients were enrolled to receive QL1706 5 mg/kg plus beva 15 mg/kg Q3W. In part 2, pts were randomized to receive QL1604 200 mg or QL1706 5 mg/kg plus beva 15 mg/kg Q3W. In part 3, pts were enrolled to receive QL1706 7.5 mg/kg plus beva 15 mg/kg Q3W. Initiation of part 3 was to be determined based on factorial analysis on the results from parts 1 and 2. Each treatment cycle lasted for 21 days. Treatment continued until disease progression or other discontinuation events. The primary endpoint was safety. Secondary endpoints included efficacy etc.

Results: As of data cutoff (18 Nov 2022), 76 pts were enrolled in parts 1 and 2 (QL1706: 50; QL1604: 26). The baseline characteristics were balanced between the 2 groups. A total of 43 (86%) pts and 23 (88.5%) pts in QL1706 and QL1604 groups experienced TRAEs. For both groups (QL1706 vs QL1604), the most common TRAEs were platelet count decreased (26% vs 23.1%); followed by AST increased (22% vs 19.2%). A total of 10 (34%) pts and 10 (38.5%) pts in QL1706 and QL1604 groups experienced Gr 3 TRAEs. A total of 25 (50%) pts and 5 (19.2%) pts in QL1706 and QL1604 groups experienced Gr 4 TRAEs. In the efficacy evaluable population, the ORR was 38.3% (18/47) and 15.4% (4/26) in QL1706 and QL1604 groups. The DCR was 74.5% and 69.2% in QL1706 and QL1604 groups. The mPFS was 6.7 months (95% CI: 3.0-11.4) and 5.4 months (95% CI: 2.4-8.5) in QL1706 and QL1604 groups. The mOS was not reached. Conclusions: QL1706 5 mg/kg showed comparable safety profile and numerically higher ORR and longer mPFS vs QL1604 when combined with beva as first-line treatment in pts with aHCC. Ph III head-to-head clinical trial to compare QL1706 or anti-PD-1/PD-L1 Ab plus beva in this population has been planned. Clinical trial information: NCT05603039. Research Sponsor: Qilu Pharmaceutical Co., Ltd.
Efficacy of lenvatinib (LEN) vs sorafenib (SOR) in the first-line (1L) treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC): A post hoc analysis of patients with nonviral etiology from REFLECT.

Ari David Baron, Carlos López López, Stephen Lam Chang, Fabio Piscaglia, Zahra Ramji, Min Ren, Kasey Estenson, Arndt Vogel, Pierre Gholam; Sutter/California Pacific Medical Center, San Francisco, CA; Marqués de Valdecilla University Hospital, IDIVAL, Santander, Spain; The Chinese University of Hong Kong, Shatin, Hong Kong; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; Eisai Inc., Nutley, NJ; Hannover Medical School, Hannover, Germany; Case Western Reserve University School of Medicine, Cleveland, OH

Background: The randomized phase 3 REFLECT trial demonstrated that LEN was non-inferior to SOR in overall survival (OS; primary endpoint) in 1L uHCC (median: 13.6 months [95% CI, 12.1–14.9] vs 12.3 months [95% CI, 10.4–13.9]) (HR, 0.92; 95% CI, 0.79–1.06). Median progression-free survival (PFS) by independent imaging review (IIR) per mRECIST was 7.3 months (95% CI, 5.6–7.5) for pts in the LEN arm and 3.6 months (95% CI, 3.6–3.7) for pts in the SOR arm (HR, 0.64; 95% CI, 0.55–0.75; p<0.0001). Objective response rate (ORR) by IIR per mRECIST was 40.6% for pts in the LEN arm and 12.4% for pts in the SOR arm (odds ratio, 5.01; 95% CI, 3.59–7.01; p<0.0001) [Kudo 2018, Lancet]. Since REFLECT, combination therapies with immunotherapy have become part of the therapeutic arsenal for the treatment of uHCC, and many studies are ongoing. Recent data suggest that viral/nonviral etiology may impact treatment outcomes [Pfister 2021, Nature; Rimini 2022, ESMO Open]. To add to the current body of evidence, this post hoc analysis evaluated efficacy in pts with nonviral etiology in REFLECT.

Methods: In REFLECT, pts with uHCC who had not received treatment for advanced disease were randomized to LEN (12 mg/day for bodyweight ≥60 kg; 8 mg/day for bodyweight <60 kg) or SOR (400 mg twice-daily) in 28-day cycles. This post hoc analysis included pts without hepatitis B or C (based on medical history) who were randomized to receive LEN or SOR. PFS, ORR (by IIR per mRECIST), and OS were analyzed. OS and PFS were estimated with the Kaplan-Meier method. Results: Of 478 pts randomized to LEN and 476 pts randomized to SOR, 127 and 108 pts, respectively, had nonviral etiology. Among randomized pts with nonviral etiology, median OS was 13.8 mos (95% CI, 10.5–18.7) in the LEN arm and 13.9 months (95% CI, 11.7–17.5) in the SOR arm (HR, 1.03; 95% CI, 0.75–1.43). Median PFS was 7.4 months (95% CI, 5.5–8.7) in pts randomized to LEN with nonviral etiology and 4.0 months (95% CI, 3.6–5.5) in pts randomized to SOR with nonviral etiology (HR, 0.60; 95% CI, 0.42–0.87). ORR was 39.4% (95% CI 30.9–47.9) in pts randomized to LEN with nonviral etiology and 20.4% (95% CI 12.8–28.0) in pts randomized to SOR with nonviral etiology. Fewer (n=34 [26.8%]) pts with nonviral etiology randomized to LEN received anticancer medication during survival follow-up than those randomized to SOR (n=46 [42.6%]). Conclusions: In this post hoc analysis, OS, PFS, and ORR in pts randomized to LEN with nonviral etiology were consistent with the overall population of pts randomized to LEN. This post hoc analysis, along with the results of the primary analysis of REFLECT [Kudo 2018, Lancet], demonstrates the efficacy of LEN regardless of etiology in uHCC, and supports LEN as a standard of care option for pts with 1L uHCC. Treatment efficacy by etiology should be assessed prospectively in future uHCC trials. Clinical trial information: NCT01761266. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
Safety and efficacy of transarterial chemoembolization combined with tyrosine kinase inhibitors and camrelizumab in the treatment of patients with advanced unresectable hepatocellular carcinoma.

Jinpeng Li, Yuntao Jia, Huihui Han, Yanyan Lin, Jinlong Song; Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China; Shandong Cancer Hospital and Institute, Jinan, shandong, China; Shandong Cancer Hospital and Institute, Jinan, China

Background: Combined systemic and local therapy is a promising treatment strategy for patients with advanced hepatocellular carcinoma (HCC). Transarterial chemoembolization (TACE), tyrosine kinase inhibitors (TKI) and PD-1 antibodies are all recommended for patients with unresectable HCC (uHCC). This study was aimed to evaluate the efficacy and safety of TACE combined with TKIs and camrelizumab in the treatment of uHCC. Methods: In this multicenter, single-arm phase II trial (ChiCTR2000039508), patients with intermediate-stage uHCC who had a Child-Pugh score ≤ 7 and had not received prior systemic anti-cancer treatment would receive treatment with TACE followed by immunotherapy with camrelizumab 200 mg every 3 weeks plus a TKI agent selected from lenvatinib (12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight <60 kg), sorafenib 400 mg bid or donafenib 200 mg bid until intolerable toxicity or disease progression. During the study treatment, patients assessed as eligible for resection would undergo surgery. The primary endpoint was objective response rate (ORR) per modified RECIST. Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), duration of response (DOR) and overall survival (OS). Results: From September 2020 to November 2021, 87 patients (81 men and 6 women; median age, 56 years) were enrolled. Among them, 43 (49.4%) patients had extrahepatic metastases, and 65 (74.7%) patients had HBV infection. As of September 28, 2022, the median duration of follow-up was 13.6 (0.83-24.9) months. A total of 34 patients (39.1%) died, and the median OS was not reached. The median PFS was 10.5 months (95% CI: 7.8-13.1). The ORR rate was 71.3% (62/87), and the DCR rate was 89.7% (78/87) per mRECIST. According to RECIST version 1.1, the ORR rate was 35.6% (31/87), and the DCR rate was 87.4% (76/87). The ORR and PFS showed consistent benefits in subgroups based on ECOG score, HBV infection, baseline alpha-fetoprotein level, combined TKI, and the number of TACE treatments. Ten patients (11.5%) successfully underwent conversion therapy and all achieved R0 resection. Two patients achieved a complete pathological response (pCR) and four achieved a major pathological response (MPR). The most common AEs were hypoproteinemia (92%), elevated lactate dehydrogenase (80.5%), elevated glutamic oxaloacetic transaminase (79.3%), elevated bilirubin (78.2%), abdominal pain (62.1%), nausea (33.3%), and RCCEP (26.4%). The incidence of grade 3-4 adverse reactions was 67.8%, and no treatment-related deaths occurred. Conclusions: TACE combined with TKI and camrelizumab showed promising clinical benefits. It can effectively control tumor progression and provide opportunities for resection with acceptable safety, which will bring great benefits to uHCC. Clinical trial information: ChiCTR2000039508. Research Sponsor: Jiangsu Hengrui Medicine.
Safety and efficacy of allogeneic natural killer cells in combination with pembrolizumab in patients with chemotherapy-refractory biliary tract cancer: A multicenter open-label phase 1/2a trial.

Galam Leem, Sung Ill Jang, Jae-Hee Cho, Jung Hyun Jo, Hee Seung Lee, Moon Jae Chung, Jeong Youp Park, Seungmin Bang, Da-Kyung Yoo, Hyo-Cheon Cheon, Jae-Eun Kim, Kyeong-Pill Lim, In-Hye Jung, Jung-Min Im, Yong Yoon Chung, Seung Woo Park; Yonsei University College of Medicine, Severance Hospital, Seoul, South Korea; Yonsei University College of Medicine, Seoul, South Korea; Yonsei University College of Medicine, Seodaemun-Gu, South Korea; SMT bio, Seoul, South Korea; SMT bio Co.Ltd, Seoul, South Korea

Background: This study investigated the administration of combination therapy, allogeneic natural killer (NK) cells and pembrolizumab, in the treatment of advanced biliary tract cancer to determine the safety and tolerability (phase 1), and the efficacy and safety (phase 2a).

Methods: Forty patients (phase 1, n=6; phase 2a, n=34) were enrolled between December 2019 and June 2021. The patients were inoperable and no further conventional chemotherapy was anticipated after finishing at least one chemotherapy. The patients received 3x10^6 NK cells/kg of highly activated allogeneic NK cells ("SMT-NK") on weeks 1 and 2 and 200 mg of pembrolizumab (Keytruda) on week 1. No treatment was given in week 3. This 3-week schedule (1 cycle) was repeated until confirmed disease progression, intolerable adverse events (AEs), patient withdrawal of consent, or finishing the maximum treatment schedule. The tumor response was evaluated after every three cycles.

Results: In phase 1, 4 patients (66.7%) experienced 7 AEs, but no severe AEs directly related to the combination of the two drugs was observed. In phase 2a, 126 AEs occurred in 29 patients (85.3%). Severe AEs (\geq grade 3) were reported in 16 patients (47.1%). No dose limiting toxicity was reported. The overall response rate (ORR) was 17.4% in the full-analysis set and 50.0% in the per-protocol set. Conclusions: SMT-NKs plus pembrolizumab resulted in no severe AEs directly related to the drug combination. The combination therapy also exerted antitumor activity with improved efficacy compared to recent monotherapy with pembrolizumab in patients with advanced biliary tract cancer. A multi-center, randomized, placebo-controlled, open-label, phase 2b clinical trials to evaluate the antitumor activity of combination therapy of SMT-NKs and pembrolizumab versus pembrolizumab monotherapy in patients with advanced biliary tract cancer is now ongoing with the aim of enrolling 128 patients (ClinicalTrials.gov identifier: NCT05429697). To date, 38 patients have been enrolled and randomly assigned to each group. Within the median follow up period of 5.3 months, the disease control rate (DCR, complete response + partial response) was 27.2% in the combination therapy of SMT-NKs and pembrolizumab group, and 7.1% in the pembrolizumab monotherapy group. The ORR was 54.5% in the combination therapy group and 42.9% in the monotherapy group. So far, no severe drug-related AEs was reported. Clinical trial information: NCT03937895. Research Sponsor: SMT Bio Co.
Economic evaluation for the US of durvalumab plus gemcitabine and cisplatin (DGC) in advanced biliary tract cancer (BTC).

Osama Aqel, Yunrong Shen, Ibrahim Alfayoumi, Ivo Abraham; Center for Health Outcomes and PharmacoEconomic Research, University of Arizona, Tucson, AZ; University of Arizona of Pharmacy, Department of Pharmacy Practice and Science, Tucson, AZ

Background: BTCs are a group of relatively rare malignancies comprised of intrahepatic cholangiocarcinoma (CCA), extrahaepatic CCA, and gallbladder cancer. The first-line standard of care of gemcitabine and cisplatin (GC) has remained unchanged for the past decade, highlighting the need for novel therapies. The TOPAZ-1 trial demonstrated improved progression-free (PFS) and overall survival (OS) with durvalumab added to GC. This trial-based economic evaluation estimated the cost-effectiveness/utility of DGC versus GC from a US payer perspective. Methods: A three state partitioned survival model (Progression-free, Progressed, Death) was developed to compare costs and overall survival outcomes associated with both treatments. PFS and OS curves were digitized, and parametric functions fitted. A 5-year time horizon with a 3% discount rate/year was considered. Costs of treatment (average sales price), administration, and monitoring parameters were sourced from Centers for Medicare & Medicaid Services databases; costs of adverse event management (grade 3/4 with rate $5\%$) were sourced from prior BTC economic evaluations. Life years (LY), quality adjusted life years (QALY), incremental cost-effectiveness and utility ratios (ICER/ICUR) were estimated in a base case (BCA) and probabilistic sensitivity analyses (PSA). A cost-effectiveness acceptability curve (CEAC) was plotted to determine the probability of either treatment being cost-effective over the other at different willingness to pay (WTP) thresholds. Results: Exponential regression was used to extrapolate DGC and GC survival curves. As shown in the table, the BCA (PSA) shows an incremental cost of DGC over GC of 131,350 (131,212), incremental LY of 0.38 (0.38), and incremental QALY of 0.26 (0.28). The BCA and (PSA) ICERs reveal an additional 345,658 (345,295) per LY gained (g) and an additional 505,192 (468,614) per QALYg. The CEAC curve shows that DGC treatment has a 50% probability of being cost-effective at a WTP threshold value of 525,000 and 100% probability at a threshold of 1,375,000 or above. Conclusions: This economic evaluation demonstrates that, in the setting of advanced BTC, DGC is associated with a slight improvement in LY and QALY, yet at a marked incremental cost, requiring a very high WTP threshold. Research Sponsor: None.

\[
\begin{array}{ccc}
\text{BCA (PSA).} & & \\
\text{Cost} & \text{GC} & \text{DGC} & \text{Difference} \\
$ & $15,716 & $147,066 & $131,350 ($131,212) \\
& ($15,812) & ($147,024) & \\
\text{LY} & 1.07 (1.07) & 1.45 (1.45) & 0.38 (0.38) \\
\text{QALY} & 0.74 (0.77) & 1.00 (1.05) & 0.26 (0.28) \\
\text{ICER} & $345,658/\text{LY}g & ($345,295/\text{LY}g) & \\
\text{ICUR} & $505,192/\text{QALY}g & ($468,614/\text{QALY}g) & \\
\end{array}
\]

Interpretation of ICER and ICUR: incremental cost to gain resp. 1 LY or 1 QALY.
Tislelizumab (TIS) versus sorafenib (SOR) in first-line (1L) treatment of unresectable hepatocellular carcinoma (HCC): The RATIONALE-301 European/North American (EU/NA) subgroup.

Arndt Vogel, Tim Meyer, Eric Assenat, Mariona Calvo Campos, Songzi Li, Yaxi Chen, Frederic Boisserie, Ramil Abdurashitov, Donatella Marino, Richard S. Finn; Hannover Medical School, Hannover, Germany; Royal Free Hospital NHS Trust, London, United Kingdom; Montpellier University Hospital, Montpellier, France; Institut Català d'Oncologia, Hospital Duran i Reynals and IDIBELL, L’Hospitalet de Llobregat, Barcelona, Spain; BeiGene (Ridgefield Park) Co., Ltd., Ridgefield Park, NJ; BeiGene (Beijing) Co., Ltd., Beijing, China; BeiGene Co., Ltd., Fulton, MD; Ordine Mauriziano Hospital, Turin, Italy; University of California Los Angeles, Los Angeles, CA

Background: HCC is one of the most commonly diagnosed cancers globally. Most cases occur in Asia, although a number of patients (pts) are affected in Europe and North America. In the phase 3, open-label RATIONALE-301 trial (NCT03412773), TIS, a PD-1 inhibitor, showed non-inferior overall survival (OS) versus SOR (hazard ratio 0.85, 95% CI: 0.71, 1.02), and a favorable safety profile, in 1L treatment of pts with unresectable HCC. Here, efficacy and safety of TIS versus SOR in the RATIONALE-301 EU/NA subgroup were compared with the overall population (OP).

Methods: Systemic therapy-naïve adults with histologically confirmed HCC were randomized (1:1) to receive TIS (200 mg IV Q3W) or SOR (400 mg orally BID) until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS; secondary endpoints included objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR) by blinded independent review committee per RECIST v1.1, and safety. Results: In the EU/NA subgroup (172/674 pts randomized), at data cutoff (July 11, 2022), median (m) OS follow-up was 37.9 months (mo) (TIS) vs 38.5 mo (SOR). At baseline, fewer pts in the EU/NA subgroup had Barcelona Clinic Liver Cancer (BCLC) Stage C disease (70% vs 78%) and extrahepatic spread (51% vs 62%), and more had a non-viral etiology (60% vs 24%) or underlying HCV infection (28% vs 13%) than in the OP, respectively. Distribution of other baseline characteristics was generally similar between the EU/NA subgroup and the OP. Efficacy data in the EU/NA subgroup were consistent with the OP. Numerically longer mOS and mDoR, higher ORR, and similar mPFS were observed with TIS versus SOR in the EU/NA subgroup. In the EU/NA safety population, incidence of ≥grade 3 treatment-emergent adverse events (TEAEs; 46% vs 66%), ≥grade 3 treatment-related TEAEs (TRAES; 17% vs 50%), and TRAEs leading to discontinuation (9% vs 15%) was lower with TIS versus SOR, respectively, similar to the OP. Conclusions: In the RATIONALE-301 EU/NA subgroup, mOS of TIS was non-inferior versus SOR, consistent with the findings from the OP. Numerically longer mOS and mDoR, and a higher ORR was seen with TIS versus SOR in the EU/NA subgroup, which had a higher rate of pts with non-viral etiology and a slightly lower number of pts with advanced-stage disease (BCLC Stage C) compared with the OP. Clinical trial information: NCT03412773.

<table>
<thead>
<tr>
<th>EU/NA subgroup</th>
<th>OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIS (n=89)</td>
<td>TIS (n=342)</td>
</tr>
<tr>
<td>SOR (n=83)</td>
<td>SOR (n=332)</td>
</tr>
<tr>
<td>OS, mo (95% CI)</td>
<td>OS, mo (95% CI)</td>
</tr>
<tr>
<td>18.3 (11.0, 26.6)</td>
<td>15.9 (13.2, 19.7)</td>
</tr>
<tr>
<td>13.7 (8.5, 19.0)</td>
<td>14.1 (12.6, 17.4)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>ORR, % (95% CI)</td>
</tr>
<tr>
<td>19.1 (11.5, 28.8)</td>
<td>9.1 (5.5, NE)</td>
</tr>
<tr>
<td>2.4 (0.3, 8.4)</td>
<td>14.3 (10.8, 18.5)</td>
</tr>
<tr>
<td>mDoR, mo (95% CI)</td>
<td>mDoR, mo (95% CI)</td>
</tr>
<tr>
<td>36.1 (16.8, NE)</td>
<td>2.1 (0.1, 4.1)</td>
</tr>
<tr>
<td>3.7 (2.2, 4.3)</td>
<td>3.6 (2.2, 4.1)</td>
</tr>
</tbody>
</table>

Intent-to-treat analysis set; data cutoff: July 11, 2022.
CI, confidence interval; NE, not evaluable.

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Impact of risk factors on overall survival (OS) in patients (pts) with unresectable hepatocellular carcinoma (HCC) treated with first-line (1L) tislelizumab (TIS).

Masatoshi Kudo, Richard S. Finn, Tim Meyer, Frederic Boisserie, Songzi Li, Yaxi Chen, Rami Abdrazilov, Andrew X. Zhu, Arndt Vogel, Shukui Qin; Kindai University Faculty of Medicine, Osaka, Osaka, Japan; Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA; Royal Free Hospital NHS Trust, London, United Kingdom; BeiGene (USA) Co., Ltd., Ridgefield Park, NJ; BeiGene (Beijing) Co., Ltd., Beijing, China; BeiGene Co., Ltd., Fulton, MD; Jiahui Cancer Center, Shanghai, China; Massachusetts General Hospital, Harvard Medical School, Boston, MA; Hannover Medical School, Hannover, Germany; Cancer Center, Qinhua Medical District, General Hospital of Eastern Theater of PLA, Nanjing, China

Background: TIS is a monoclonal antibody with high affinity and specificity for programmed cell death protein 1. In the phase 3 RATIONALE-301 trial (NCT03412773), TIS demonstrated non-inferior OS versus sorafenib (SOR) as 1L monotherapy for unresectable HCC (median [m] OS 15.9 [TIS] vs 14.1 [SOR] months [mo]; hazard ratio [HR] 0.85), with a favorable safety profile. Certain biomarkers are potential prognostic factors and may impact OS in 1L treatment of unresectable HCC; this exploratory analysis examined the effect of albumin-bilirubin (ALBI) grade, platelet count, platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) as predictors of OS in RATIONALE-301.

Methods: Systemic therapy-naïve adults with histologically confirmed HCC (Barcelona Clinic Liver Cancer Stage C or Stage B that was not amenable to or progressed after loco-regional therapy; Child-Pugh A), with ≥1 measurable lesion per RECIST v1.1, and an ECOG performance status ≤1 were randomized 1:1 to receive TIS (200 mg IV Q3W) or SOR (400 mg orally BID) until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS. Results: Overall, 674 pts were randomized (TIS n=342; SOR n=332). At data cutoff (July 11, 2022), minimum study follow-up was 33 mo. Demographic and baseline characteristics for biomarkers were generally balanced across arms. Numerically longer (≥2 mo) mOS was observed in biomarker subgroups ALBI grade 1 vs 2 and NLR ≤3 vs >3 with TIS or SOR, and PLR ≤141 vs >141 with TIS. Both platelet count threshold subgroups were accompanied by a smaller difference (<2 mo) in mOS between biomarker cutoffs, which may indicate limited prognostic value for this biomarker. TIS also demonstrated numerically longer OS versus SOR in the same subgroup categories: ALBI grade 1, PLR ≤141, and NLR ≤3. Conclusions: This analysis suggests that ALBI grade, PLR, and NLR could have prognostic value for OS, irrespective of treatment. TIS demonstrated numerically improved mOS compared with SOR for PLR ≤141 and NLR ≤3, suggesting higher benefit for pts with a more favorable balance between systemic inflammation and immunity. Clinical trial information: NCT03412773. Research Sponsor: BeiGene, Ltd.; This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Adeline Lum Nde, PhD, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

<table>
<thead>
<tr>
<th>No. events/ No. pts</th>
<th>HR for death (95% CI)</th>
<th>Median OS (mo) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBI grade</td>
<td></td>
<td>TIS</td>
</tr>
<tr>
<td>2</td>
<td>156/180</td>
<td>0.84 (0.61, 1.16)</td>
</tr>
<tr>
<td>3</td>
<td>340/482</td>
<td>0.85 (0.69, 1.06)</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;150K</td>
<td>281/378</td>
<td>0.88 (0.66, 1.16)</td>
</tr>
<tr>
<td>≤150K</td>
<td>215/284</td>
<td>0.83 (0.63, 1.08)</td>
</tr>
<tr>
<td>NLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>204/264</td>
<td>0.90 (0.68, 1.19)</td>
</tr>
<tr>
<td>≤3</td>
<td>292/398</td>
<td>0.79 (0.63, 1.00)</td>
</tr>
<tr>
<td>NLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>198/249</td>
<td>0.98 (0.74, 1.30)</td>
</tr>
<tr>
<td>≤3</td>
<td>298/413</td>
<td>0.74 (0.59, 0.93)</td>
</tr>
</tbody>
</table>

No. = number of events. Intent-to-treat analysis set.

*Threshold used in RATIONALE-208.
A novel patient-centric longitudinal data registry platform to generate insights into real-world cholangiocarcinoma (CCA) clinical practice.

Amanda Nottke, Milind M. Javle, Nilofer Saba Azad, Elise Brimble, Richard L Martin, Conner O'Brien, Stacie Lindsey, Melinda Bachini, Shishir K. Maithel; Invitae, San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic Arizona, Scottsdale, AZ; Johns Hopkins University, Chevy Chase, MD; Cholangiocarcinoma Foundation, Salt Lake City, UT; Winship Cancer Center of Emory University, Atlanta, GA

Background: Treatment of advanced CCA has changed dramatically over the past five years with the advent of molecularly targeted therapy, now approved in the 2nd line and beyond. However, real world utilization of molecular profiling and targeted therapy is still unknown and these data are critical to empower treatment decision-making. Methods: In 2019, the Cholangiocarcinoma Foundation (CCF) and Ciitizen (a wholly owned subsidiary of Invitae Corporation) collaboratively launched a registry platform that directly consents patients and collects comprehensive medical records. De-identified data including clinical characteristics, molecular testing, interventions, and outcomes are extracted and standardized for research use. The data is longitudinal with regularly planned updates; registry participants can be re-engaged to obtain additional data and communicate tailored insights. Results: We quantified the rate of molecular testing, the presence of targetable biomarkers, and the utilization and outcomes on matched targeted therapies for 372 individuals with CCA. 328 (88.2%) individuals had molecular testing, with the identified targetable mutations and matched therapies reported. Of 328 individuals who had molecular testing, 111 (33.8%) individuals had one or more targetable mutations (116 mutations total). Only 46% (51) of individuals with targetable mutations received targeted therapy. Of the 54% (60) individuals with targetable mutations that did not receive any matched therapy, the majority (61.7%, 37) were in early disease or first line of treatment and therefore not yet eligible for targeted therapy. These individuals will be informed that based on their molecular profile, a targeted therapy may be an option, and suggest they discuss with their treating physician. Conclusions: A novel prospectively-maintained database registry for CCA has been formed in collaboration between a patient advocacy organization (CCF) and industry (Invitae). Prevalence of actionable biomarkers was higher than historically expected and may reflect patient utilization bias of the registry platform. Molecular profiling and access to targeted therapeutics remains suboptimal at this time in CCA. Future directions for the registry include identifying and targeting disparities in care and supporting biopharmaceutical development and regulatory decisions. Research Sponsor: Invitae Corporation.

<table>
<thead>
<tr>
<th>Biomarker Evaluable Cohort (n=328)</th>
<th># (%)</th>
<th># Receiving Matched Therapy</th>
<th>Matched Therapy Outcomes (mean no. days: #)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH1 R132</td>
<td>45 (13.7%)</td>
<td>12</td>
<td>ToT: 190 (14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17</td>
<td>TTP: 158 (9)</td>
</tr>
<tr>
<td>FGFR2 Fusion / Rearrangement</td>
<td>34 (10.4%)</td>
<td>15</td>
<td>TTP: 319.4 (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>TTP: 367.5 (10)</td>
</tr>
<tr>
<td>MSI-H / dMMR / TMB-H</td>
<td>25 (7.6%)</td>
<td>12</td>
<td>TTP: 368.4 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>TTP: 210.6 (5)</td>
</tr>
<tr>
<td>HER2 Positive / Amplified</td>
<td>9 (2.7%)</td>
<td>7</td>
<td>TTP: 219 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>TTP: 499.5 (2)</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>3 (0.9%)</td>
<td>2</td>
<td>TTP: 32 (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>TTP: 114 (n=1)</td>
</tr>
</tbody>
</table>

ToT: Time on Treatment; TTP: Time to Progression.
Liquid-biopsy detection of FGFR2 and other actionable rearrangements in GI malignancies.

Pashtoon Murtaza Kasi, Jessica Kim Lee, Hanna Tukachinsky, Lincoln W Pasquina, Pierre Vanden Borre, Brennan James Decker, Dean C. Pavlick, Justin Allen, Christine Parachoniak, Alexa Betzig Schrock, Christine M. Lovly, Geoffrey R. Oxnard, Vivek Subbiah; Weill Cornell Medicine, Engleman Institute of Precision Medicine, New York Presbyterian Hospital, New York, NY; Foundation Medicine, Inc., Boston, MA; Foundation Medicine, Inc., Cambridge, MA; Vanderbilt University Medical Center, Nashville, TN; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Actionable rearrangements (RE) represent an emerging therapeutic target for GI malignancies. However, there remains uncertainty whether liquid biopsy (LBx) assays testing circulating tumor DNA (ctDNA) can detect RE with the same fidelity as tissue biopsy. Here we report the performance of ctDNA-based comprehensive genomic profiling (CGP) for the detection of RE leveraging an FDA-approved >300-gene platform, with a focus on data from patients with GI malignancies. Methods: An institutional research database of clinical CGP results for tissue biopsy (TBx, FoundationOneCDx) and LBx (FoundationOneLiquid CDx) from patients with cancers of the GI tract was reviewed. Sensitivity for FGFR2 RE was studied in patients with cholangiocarcinoma (CCA) or carcinoma of unknown primary (CUP) and both TBx and LBx CGP available. Results: Across 7870 GI LBx, 1094 predicted pathogenic RE were detected in 826 cases (10%) including 283 oncogenic kinase RE, 686 inactivating RE, and 125 other gain-of-function RE. FGFR2 was the most frequently rearranged gene, enriched in CCA (4.4%, 37/833) and stomach (3.0%, 11/368). EGFR RE (38) occurred across 6 cancer types and included 8 fusions, 15 c-terminal truncations, 4 intragenic deletions/inversions, and 3 kinase domain duplications. BRAF RE (31) were detected among in colorectal (22) and pancreas (9) cases. LBx detected 44 exon 3 skipping (protein stabilizing) RE in CTNNB1 (beta-catenin) across all samples. Other frequent activating RE were detected in MYC (36), FGFR3, RET, ROS1 (21 each), and ALK (13). Potentially targetable inactivating RE were detected in BRCA1 (28), ARID1A (24), STK11 (22), PTEN (17), TSC2 (14), and BRCA2 (8). Focusing on CCA, FGFR2 RE were more prevalent in cases with elevated (>1%) ctDNA tumor fraction (TF, 26/342, 7.6%), matching the prevalence in TBx (7.8%, 505/6,492) with a similar spectrum of fusion partners seen for both TBx and LBx (30% BICC1, 70% rare for both). In 13 CCA/CUP patients positive for FGFR2 RE by TBx, LBx detected 12 (92%) including 8 different fusion partners; the false negative case had TF <1%. In 11 CCA LBx samples with FGFR2 resistance mutations detected, LBx CGP successfully detected a driver FGFR2 RE in 10 and driver C382R mutation in 1. Conclusions: Rearrangements are represented across GI malignancies, including many that result in known oncogenic drivers that may be targetable with available therapies. We observe reliable detection of FGFR2 fusions in ctDNA, in contrast to some prior publications. ctDNA represents a pragmatic analyte for detection of rearrangements and other actionable alterations, offering timely result return when tissue is inadequate or unavailable. Research Sponsor: Foundation Medicine Inc.

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th>% Colorectal</th>
<th>% Stomach, esophagus</th>
<th>% Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>833</td>
<td>2891</td>
<td>911</td>
<td>3235</td>
</tr>
<tr>
<td>Any pathogenic RE</td>
<td>152</td>
<td>406</td>
<td>14</td>
<td>209</td>
</tr>
<tr>
<td>FGFR2 RE</td>
<td>37</td>
<td>4.4</td>
<td>8</td>
<td>0.3</td>
</tr>
<tr>
<td>BRAF RE</td>
<td>2</td>
<td>0.0</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>EGFR RE</td>
<td>2</td>
<td>0.2</td>
<td>13</td>
<td>0.4</td>
</tr>
<tr>
<td>RET/ROS1/ALK RE</td>
<td>2</td>
<td>0.2</td>
<td>27</td>
<td>0.9</td>
</tr>
<tr>
<td>FGFR3 RE</td>
<td>3</td>
<td>0.4</td>
<td>10</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Sintilimab plus gemcitabine and cisplatin as a first-line treatment for patients with advanced biliary tract cancer: A biomolecular exploratory, phase II clinical trial.

Zhen-gang Yuan, Tian-mei Zeng, Guang Yang, Cheng Lou, Wei Wei, Chen-jie Tao, Xi-yun Chen, Qin Han, Zhuo Cheng, Pei-pei Shang, Yu-long Dong, He-ming Xu, Lie-ping Guo, Dong-sheng Chen, Yunjie Song, Chuang Qi, Wanglong Deng; Department of Oncology, Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Department of Oncology, Eastern Hepatobiliary Surgery Hospital, the Naval Medical University, Shanghai, China; Jiangsu Simcere Diagnostics Co., Ltd, Nanjing, China

Background: The prognosis of biliary tract cancer (BTC) remains unsatisfactory. Thus, this study aimed to determine the efficacy, safety, and predictive biomarkers of the immune checkpoint inhibitor sintilimab in combination with gemcitabine and cisplatin (GemCis) in advanced BTCs. Methods: In this single-arm, phase II study (Trial registration number: ChiCTR2000036652), gemcitabine (1000 mg/m²) plus cisplatin (25 mg/m²) were administered on days 1 and 8, respectively, while 200 mg sintilimab was administered on day 1 of each 21-day cycle for 6–8 weeks, followed by sintilimab alone up to 2 years. The primary endpoint was overall survival (OS). The second endpoints were objective response rate (ORR), progression-free survival (PFS), and disease control rate, assessed using RECIST V.1.1. Multiomics biomarkers associated with clinical response were assessed as exploratory objectives. Results: Thirty patients were enrolled between August 2020 and May 2022. The median follow-up duration, OS, and PFS were 12.3 months (95% confidence interval [CI]: 9.1–16.0), 15.9 months (95% CI: 8.6–not reached), and 5.1 months (95% CI: 4.3–8.7), respectively. Here, 36.7% of patients were found to achieve an objective response. The most common grade 3 or 4 treatment-related adverse events were thrombocytopenia (33.3%), with no reported deaths nor unexpected safety events. Biomarker analysis indicated that patients with homologous recombination repair pathway gene alterations (median, PFS: 9.8 vs. 4.5 months, p = 0.023; OS: NR vs. 9.0 months, p = 0.014; ORR: 77.8% vs. 19%, p = 0.004) or loss-of-function mutations in chromatin remodeling genes (median, PFS: 8.7 vs. 4.2 months, p = 0.021; ORR: 63.6% vs. 21.1%, p = 0.046) presented better tumor response and survival outcomes. Furthermore, transcriptome analysis of the tumor immune microenvironment revealed a markedly longer PFS, and tumor response were associated with higher expression of 3-gene effector T cell signature (median, PFS: 7.8 vs. 4.3 months, p = 0.02; ORR: 64.2% vs. 7.1%, p = 0.01; ORR: 64.2% vs. 7.1%, p = 0.004). Moreover, our findings highlighted the adverse predictive value of mast cells in immuno-chemotherapy for BTCs for the first time. Conclusions: Sintilimab plus GemCis displayed a promising antitumor activity and acceptable safety profile as a first-line treatment in patients with advanced BTC. Multiomics potential predictive biomarkers are identified and warrant further verification. Clinical trial information: ChiCTR2000036652. Research Sponsor: None.
Phase II clinical trial of olaparib plus pembrolizumab in the treatment of patients with advanced biliary tract cancer.

James O’Bryan, Chao Yin, Benjamin Adam Weinberg, Marcus Smith Noel, Reetu Mukherji, Monika Kulasekaran, Seema Agarwal, Gary Kupfer, Hongkun Wang, Marion L. Hartley, John Marshall, Aiwu Ruth He, ASCO Authors’ Group; MedStar Georgetown University Hospital, Washington, DC; MedStar Harbor Hospital, Baltimore, MD; Georgetown University, Washington, DC; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; The Ruesch Center for the Cure of Gastrointestinal Cancers, Washington, DC

Background: Over 20% of biliary tract cancers (BTCs) carry mutations in homologous recombination DNA damage repair (HR-DDR) pathways. The PARP inhibitor olaparib (O) blocks tumor DNA repair and may induce response in BTCs with such mutations. Furthermore, HR-DDR mutations may engender neoantigens that improve response to immune checkpoint inhibitors. We propose that treatment with O and the anti-PD-1 monoclonal antibody pembrolizumab (P) will produce a durable anti-tumor response to BTC, especially in patients with HR-DDR mutations.

Methods: Consent for participation was obtained. Eligibility criteria included age ≥ 18 years with an ECOG score of ≤1 and a histologic diagnosis of advanced or metastatic BTC with progression of disease (PD) on prior first-line therapy. Treatment featured oral O (300 mg twice daily) plus intravenous P (200 mg every 3 weeks). Response was measured radiographically using RECIST 1.1 guidelines. The primary endpoint was overall response rate (ORR), with the alternative hypothesis that O + P would improve ORR compared to historical controls (versus the null hypothesis of no improvement). Type I and II error rates were set at 5% and 15%, respectively. Simon’s optimal two-stage design was used. Planned sample size was 13 patients in the first stage. Continuation to the second stage would only occur if ≥3 patients demonstrated response. The second stage was planned to include 20 additional patients (N = 33 total), which was based on the number needed to demonstrate an improvement in ORR from 17.5% in historical controls to at least 35.0%. Results: Of 21 eligible patients, 14 were accrued between June 2020 and March 2022, and 13 were evaluable for efficacy. Patients had a median age of 63 years, were primarily female (71%), Caucasian (50%), and with metastatic disease (93%). Patients received a mean of 6.5 cycles of therapy. Best treatment response included partial response (N = 2), stable disease (N = 5), and PD (N = 6). The ORR was 15.3% (95% CI = 0.02-0.45). Of the partial responders, 1 patient achieved a duration of response of 8 months (mos), and 1 has ongoing response at 24 mos. Median (med) time to progression was 7.7 mos (95% CI = 1.2-9.3), med progression free survival was 5.5 mos (95% CI = 1.2-7.7), and med overall survival was 11.9 mos (95% CI = 5.5-15.4). Most patients (64%) developed at least one treatment-related adverse event (trAE). Grade 3 trAEs were experienced in 5 patients (36%) and included anemia (N = 3), diarrhea (N = 1), and transaminitis (N = 1). Conclusions: While O + P has acceptable safety and toxicity, the study did not achieve significant improvement in the primary endpoint. However, the two patients who demonstrated durable treatment response were found to have HR-DDR tumor mutations (including RAD51, ATM, and BRCA2), necessitating further research into the efficacy of O + P for patients with similar tumor genomes.

Characterizing KRAS allele variants within biliary tract cancers.

Gordon Taylor Moffat, Zishuo Ian Hu, Anaemy Danner De Armas, Jeffrey S. Ross, Milind M. Javle, Jennifer J. Knox; Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; University of Texas MD Anderson Cancer Center, Houston, TX; SUNY Upstate Medical University, Syracuse, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; Princess Margaret Cancer Centre, Toronto, ON, Canada

**Background:** Biliary tract cancers (BTC) are aggressive malignancies with a poor 5-year survival rate and growing incidence globally. KRAS mutations (mut) in BTC are associated with a poor prognosis; however, PD-L1 inhibition with Durvalumab may lead to an improved survival with KRAS mut (TOPAZ-1 trial). It is important to understand the genomic landscape and immunophenotype of KRAS mut in BTC given the advent of immunotherapeutics and small molecular inhibitors targeting KRAS mut. **Methods:** A retrospective pooled analysis was performed from the following patient databases: Princess Margaret Cancer Centre, MD Anderson Cancer Center, Foundation Medicine, along with the publicly accessible cBioPortal for Cancer Genomics that includes the American Association for Cancer Research Project Genie cancer registry of real-world data assembled between 19 leading international cancer centers. Any overlapping cases were excluded. Patients included had a diagnosis of a BTC and completed molecular testing from January 2017 to December 2022. Cohort demographics, KRAS allelic variants, concurrent genetic aberrations, and immune biomarkers (PD-L1, TMB, MSI and gLOH) were summarized. Log-rank, Wilcoxon, and Kaplan-Meier tests were conducted for survival analysis. **Results:** 5,813 BTC patients were included, and 1000 patients (17.2%) had a KRAS mutation. The prevalence of KRAS mut was higher in extra-hepatic cholangiocarcinoma (EH-CCA) (36.1%) and perihilar (PH)-CCA (28.6%) than in intra-hepatic (IH)-CCA (11.82%) and gallbladder cancer (GBC) (7.6 %). The most common KRAS allelic variant was G12D, and the most common co-mutation was TP53, except in PH-CCA, which was G12V and SMAD4, respectively. In this cohort, race was primarily White (73%). The most prevalent variant in North America was G12D, while G12V and Q61H were more prevalent with genomic African American and genomic East Asian descent, respectively. For patients with KRAS mut, GBC had the most PD-L1 high positivity (17%) compared to IH-CCA (7%) and EH-CCA (3%), along with the most MSI-H phenotypes and the highest mean and median TMB compared to other sites, especially in G12V and Q61H variant patients. Genomic loss of heterozygosity was low among all groups. In the survival analysis, patients with the G12V allele subtype had the lowest OS at 17.8 months, followed by Q61H (22.8 months) and G12D (25.1 months) (p = 0.022). Survival analysis with KRAS co-mut (TP53, SMAD4, CDK2NA, or additional KRAS mut) was not significant (p = 0.7). In a co-variance analysis of KRAS variants and tumour site, there was no difference in IH-CCA and GBC but lower OS in Q61H variants in PH-CCA and G12V variants in EH-CCA (p = 0.0081). **Conclusions:** This large series adds to the growing body of comprehensive genomic and immune landscape data of KRAS mut in BTC and will be of value in planning specific therapies in this heterogeneous group. Immune profiling studies are ongoing to further describe the immunophenotype of this subset. Research Sponsor: None.
Trastuzumab (T) plus gemcitabine-cisplatin (GC) for treatment naïve HER2 positive biliary tract adenocarcinomas (BTC): A multicentre open-label, phase II study (TAB).

Vikas S. Ostwal, Sarika Mandavkar, Prabhat Ghanshyam Bhargava, Sujay Srinivas, Chaitali Nashikkar, Omshree Shetty, Rajiv Kumar Kaushal, Subhash Yadav, Aekta Shah, Akshay Dwarka Bahteti, Suman Kumar Ankathi, Daksha Mehta, Akhil Kapoor, Mahesh Goel, Shraddha Patkar, Deepali Chaugule, Anant Ramaswamy; Tata Memorial Hospital (HBNI), Mumbai, India; Tata Memorial Centre, (HBNI), Mumbai, India; Homi Bhabha Cancer Hospital, Varanasi, Varanasi, India; Tata Memorial Center (HBNI), Mumbai, India; Tata Memorial Centre (HBNI), Mumbai, India

Background: HER2 over-expression or amplification is seen in 4%-16% of BTCs and is a therapeutic target of interest. Gemcitabine-cisplatin (GC) is one of the standard regimens of choice in advanced BTCs. We aimed to evaluate the clinical activity of GC plus anti-HER2 antibody trastuzumab as initial treatment in HER2-positive BTC. Methods: This study was an investigator-initiated, open-label, single-arm, multi institutional, phase II trial in patients (pts) aged 18 years or older with HER2-positive (defined as IHC 3+ or IHC 2+ and FISH positive), treatment naïve BTCs. Patients received GC (Gem 1000 mg/m2 IV and Cisplatin 25mg/m2 IV on day 1 and 8, q 3 weeks) combined with Trastuzumab at 8mg/kg as initial dose followed by 6mg/kg q 3-weekly till disease progression (PD) or unacceptable toxicities. The primary end-point of the study was an improvement in 6-month progression free survival (PFS) from 40% (historical cohort) to 60% in the study arm. Next generation sequencing to evaluate HER2 and other mutations was conducted on the tissue samples of the patients screened for this study.

Results: From March 2020 to August 2022, of the 876 patients were screened for HER2 status, 118 (13.4%) were found to have HER2 positive status and 90 of them were enrolled into the study. A majority of patients had GBC (95.6%) and at least 2 sites of metastatic disease beyond primary (77.8%). With a median follow up of 8.5 months, 72 patients had PD and the median PFS was 7.95 months (95% CI: 6.84 - 9.06); median overall survival (OS) was 9.95 months (95% CI: 9.25 – 10.66). Partial responses (PR) were seen in 8 patients (8.9%) and 61 had stable disease (67.7%) for a disease control rate of 76.6%. Common chemotherapy-related grade 3 or 4 adverse events were anemia [26 (28.9%)], neutropenia [18(20%)] and thrombocytopenia [8(8.9%)] while one patient has Trastuzumab related asymptomatic fall in cardiac ejection fraction (=10%). The presence of isolated TP53 mutations predicted for inferior PFS compared to patients with other mutations (TERT promoter, HER2, PIK3CA etc) or no detected mutations (6.51 months vs. 12.02 months vs. 10.58 months; p<0.001). Conclusions: The combination of GC and trastuzumab shows near doubling of survival in treatment naïve HER2 positive BTC in a prospective manner for the first time and sets the stage for a larger phase III trial with the combination. Evaluating mutations like TP53, HER2, TERT promoter and PIK3CA along with HER2 testing could be considered as a preferred modality to select these patients for anti HER2 therapy. Clinical trial information: CTRI/2019/11/021955. Research Sponsor: Educational grants to the institute from reddy's lab pt ltd for this study.

<table>
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<th>Mutational spectrum</th>
<th>Individual mutations</th>
<th>Frequency (%)</th>
<th>Median PFS (range)</th>
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<td>FGF1R 1 (1.1)</td>
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<td>PIK3CA 5 (5.6)</td>
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Individual patient-level data validation of surrogate and modified endpoints for immunotherapy in advanced hepatocellular carcinoma: Post-hoc analysis of IMbrave150 and real-world observations.

Mir Lim, Maishara Muquith, Bernadette Miramontes, Chieh-Ju Lee, Yi-Hsiang Huang, David Hsiehchen; UT Southwestern Medical Center, Dallas, TX; University of Texas Southwestern Medical Center, Dallas, TX; Taipei Veterans General Hospital, Taiwan, Taiwan; Taipei Veterans General Hospital, Bei Tou Qu, Taiwan

Background: Immune checkpoint inhibitors (ICIs) have become the preferred treatment for advanced hepatocellular carcinoma (HCC). Surrogate endpoints including overall response rate (ORR) and progression-free survival (PFS) are preferred outcome measures in early-phase trials. However, ICIs can induce atypical patterns of response and progression, calling into question the validity of surrogate endpoints as predictive of overall survival (OS) benefit. We performed a post-hoc analysis of a large, randomized phase 3 clinical trial (IMbrave150) and cross-sectional analysis of a multi-institution real-world environment (RWE) to assess the OS surrogacy of ORR and PFS using Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), or immune-modified RECIST (imRECIST) in patients treated with ICIs.

Methods: The IMbrave150 cohort in our analysis included 279 out of 336 patients treated with atezolizumab and bevacizumab in the intent-to-treat population. The RWE cohort included 328 patients with Child-Pugh A or B disease treated in the first or subsequent-line setting with anti-PD-1/L1 therapies. RECIST, mRECIST, and imRECIST ORR and PFS data for the IMbrave150 cohort was determined by investigators and central review, while RECIST ORR and PFS data for the RWE cohort was determined by treating providers or retrospective review.

Results: In the IMbrave150 and RWE cohorts, Child-Pugh A patients treated in the first-line setting with CR/PR showed greater OS versus patients with SD/PD (IMbrave150: HR 0.16, 95% CI 0.10-0.26; RWE: HR 0.25, 95% CI 0.15-0.43). CR was associated with the greatest OS benefit, followed by PR, SD, and PD. Patients treated in the second-line setting or with Child-Pugh B disease showed that ORR was able to discriminate OS benefit but hazard ratios were closer to the null. In both cohorts, there was a positive rank correlation between RECIST PFS and OS (IMbrave150: Kendall’s $\tau = 0.44$, p < 0.001; RWE: Kendall’s $\tau = 0.52$, p < 0.001). However, only 31-46% of the variance in OS rankings was explained by PFS rankings. mRECIST PFS and imRECIST PFS showed a positive rank correlation with OS, with an explained variance of 30% and 38% for mRECIST and imRECIST, respectively.

Conclusions: Our results suggest that RECIST ORR is a robust surrogate endpoint in HCC treated with ICIs. In contrast, the explained variance between RECIST PFS and OS in both the IMbrave and RWE cohorts was limited. This may reflect the impact of ICIs on response to subsequent therapies which may extend OS benefit. Although prior studies have proposed that modifications to RECIST may lead to more accurate surrogate markers, mRECIST and imRECIST ORR or PFS in HCC treated with ICIs were not associated with greater predictive performance compared to RECIST. Research Sponsor: None.
Salvage ipilimumab plus nivolumab in advanced hepatocellular carcinoma after prior anti-PD-(L)1 blockade.

Stephanie Leigh Alden, Mir Lim, Chester Kao, Daniel Shu, Amit G. Singal, Anne M. Noonan, Paige Griffith, Marina Baretti, Won Jin Ho, Ihab R. Kamel, Mark Yarchoan, David Hsiehchen; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD; University of Texas Southwestern Medical Center, Dallas, TX; Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX; The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Combination PD-(L)1/CTLA-4 blockade is approved in patients with advanced hepatocellular carcinoma (HCC) in the first line or after treatment with sorafenib, but it is unclear if combination therapy has efficacy after treatment with anti-PD-(L)1 alone or in combination with a multikinase inhibitor. We evaluated responses to ipilimumab plus nivolumab in patients with advanced HCC who previously received anti-PD-(L)1 to assess the efficacy and safety of this regimen. Methods: We performed a multi-center retrospective review of patients 18 years of age or older with a diagnosis of HCC based on histology or imaging who had received at least one dose of anti-PD-(L)1 therapy prior to receiving ipilimumab plus nivolumab as a subsequent line of therapy. All patients had imaging and/or laboratory monitoring to monitor for disease progression. Results: Our cohort contained 32 patients, with a majority being male (88%, n = 28) and a median age of 67 years. All patients were Child Pugh A (66%, n = 21) or B (34%, n = 11) at the start of treatment, with most having an ECOG performance status of 0-1 (84%, n = 27). The median number of prior lines of therapy was 2 (range 1-8). Prior anti-PD-(L)1 containing regimens included atezolizumab plus bevacizumab (50%, n = 16), other VEGF plus anti-PD-(L)1 combination (31%, n = 10), and anti-PD-(L)1 monotherapy (19%, n = 6). The objective response rate (ORR) was 22% (1 CR, 3%), 6 PR (19%), with remaining responses including 8 SD (25%), 16 PD (50%), and 1 NE (3%). Among patients who had an objective response to ipilimumab plus nivolumab, none had an objective response to prior anti-PD-(L)1 treatments. Response rates were similar across major clinical (obese vs. non-obese) and etiological (viral vs. non-viral) subsets of HCC. Response to ipilimumab plus nivolumab was associated with improved PFS and OS: median PFS for PD/SD/NE 2.4 months (95% CI: 2.1-NR) vs. PR/CR not reached (NR) (95% CI: 7.5-NR), p = 0.004, and OS for PD/SD/NE 5.9 months (95% CI: 3.1-NR) vs. PR/CR NR (95% CI: NR-NR), p = 0.02. Immune related adverse events (irAEs) were reported in 13 patients (41%), and 6 patients experienced grade 3-4 irAEs (19%). One patient in our cohort experienced a fatal irAE (autoimmune hepatitis), and 5 patients discontinued therapy due to irAEs. Conclusions: This study demonstrates that ipilimumab plus nivolumab has clinical activity in patients with advanced HCC who previously received anti-PD-(L)1 therapy with an acceptable safety profile, supporting this regimen as second line immune checkpoint inhibitor therapy in advanced HCC. Further studies are required to determine the optimal sequence of therapies in advanced HCC. Research Sponsor: None.
The metabolic activity assessed by $^{18}$F-FDG PET and its correlation with tumor immune status and prognosis in advanced biliary tract cancer patients treated with 1L GemCis plus durvalumab +/- tremelimumab.

Jeesun Yoon, Hyunpil Sung, Kyung-Hun Lee, Jin Won Kim, Dae-Won Lee, Tae-Yong Kim, Ju-Hee Bang, Ah-Rong Nam, Kyoung-Seok Oh, Jae-Min Kim, Yoojin Jeong, Sea Young Choo, Hyo Jung Kim, Su In Lee, Gi Jeong Cheon, Do-Youn Oh; Medical Oncology, Seoul National University Hospital, Seoul, South Korea; Department of Nuclear Medicine, Seoul National University Hospital, Seoul, South Korea; Division of Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; Medical Oncology, Seoul National University Hospital, Seoul, Korea, Republic of (South)

Background: Gemcitabine/Cisplatin (GemCis) in combination with durvalumab have been established as a global new standard of care in first-line (1L) advanced biliary tract cancer (BTC) in the TOPAZ-1 trial (Oh et al. NEJM Evid, 2022). In our phase 2 study (NCT03046862, Oh et al. Lancet Gastroenterol Hepatol, 2022) exploring GemCis/durvalumab +/- tremelimumab, dynamics of PD-L1 expression after one cycle of treatment has been suggested as a predictor for clinical outcomes. Tumor metabolic activity assessed with $^{18}$F-FDG PET is usually associated with prognosis in solid tumors. However, the role of metabolic activity in patients treated with the combination of chemotherapy and immunotherapy has not yet been much studied, in terms of correlation with tumor immune landscape and prognosis.

Methods: This study recruited 1L, advanced BTC patients in 3 different cohorts. $^{18}$F-FDG PET was conducted at baseline (pre-treatment) and at the time of first tumor response evaluation (post-treatment). Metabolic indices of the main tumor lesion were measured, including maximum standardized uptake values (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). Metabolic response evaluation was assessed according to EORTC criteria. Tumor biopsies were done at baseline and after 1 cycle of treatment. Results: Among total 124 enrolled patients, 118 patients were included in this PET analysis. The early metabolic response rate was 54.3% (mCR 10.2%, mPR 44.1%, mSD 36.4%, mPD 9.3%). Pre-treatment metabolic parameters (SUVmax, MTV, TLG) were associated with disease status, previous operation history, and CRP level. High pre-treatment SUVmax was associated with poor progression-free survival (PFS) and overall survival (OS). Low post-treatment metabolism and large reduction in metabolism between pre- and post-treatment were associated with responder (vs non-responder), long PFS and long OS. In terms of PD-L1 expression and tumor metabolism, Tumor cell (TC) PD-L1 at pre-treatment was not associated with metabolic parameters; however, high immune cell (IC) PD-L1 expression showed significant association with lower MTV and TLG. In terms of dynamics of PD-L1 and tumor metabolism, post-treatment SUVmax was higher in patients with TC PD-L1 decrease. In patients with decrease of PD-L1 on both TC and IC (worst prognostic group), smaller reduction in metabolism between pre- and post-treatment was observed than the other patients. Conclusions: In BTC patients treated with 1L GemCis plus durvalumab +/- tremelimumab, tumor metabolic activity and its dynamics conferred prognostic impact. Furthermore, tumor metabolic activity has a potential to be associated with tumor immune landscape. Clinical trial information: NCT03046862. Research Sponsor: AstraZeneca; National Research Foundation of Korea.
Genomic targetability and survival outcomes of biliary tract cancers (BTC): A retrospective cohort study of the Australian Molecular Screening and Therapeutics (MoST) program.

Subotheni Thavaneswaran, Frank Po-Yen Lin, Christine E Napier, John P. Grady, Mandy L. Ballinger, Maya Kansara, Peter S. Grimison, Nick Pavlakis, Mark Ka Wong, Katrin Marie Sjoquist, David Goldstein, Lorraine A. Chantrill, John Simes, David Morgan Thomas; Garvan Institute of Medical Research and The Kinghorn Cancer Centre, Sydney, NSW, Australia; Garvan Institute of Medical Research, Sydney, Australia; Garvan Institute of Medical Research, Sydney, Australia; Chris O’Brien Lifehouse, Sydney, NSW, Australia; Royal North Shore Hospital, Sydney University, Sydney, Australia; Westmead Cancer Care Centre, Westmead, Australia; NHMRC Clinical Trials Centre, The University of Sydney; St George Hospital, Sydney, NSW, Australia; Department of Medical Oncology, Sydney, NSW, Australia; Wollongong Hospital, NSW, Wollongong NSW, NSW, Australia; NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia; Australian Genomic Cancer Medicine Centre, Darlinghurst, Australia

Background: Despite advances in therapeutic strategies, advanced BTC continue to have poor outcomes. We examined the genomic composition of these cancers and differences in clinical outcomes based on therapies (tx) received. Methods: This study included all BTC patients (pts) undergoing comprehensive genomic profiling (CGP) through an Australia-wide precision oncology program, MoST (ACTRN12616000908437). The primary outcome was overall survival (OS) measured from start of first line (1L) systemic tx. The TOPOGRAPH knowledge base was used to determine genomic actionability of alterations identified, tiered by the strength of supportive clinical evidence. Tier 1/2 are regulatory body (TGA or FDA/EMA) approved therapies in BTC; tier 3A is supported by BTC-specific clinical evidence; 3B by clinical evidence inferred from another cancer type; 4, pre-clinical evidence. As targeted therapies are only approved in the subsequent-line setting, a further OS analysis was performed from start of second line tx (2L). Results: Between December 2016 and August 2022, 223 pts had CGP results available: 170 cholangiocarcinoma (99 intrahepatic, 46 extrahepatic, 25 unspecified primary site) and 53 gallbladder carcinomas. Of 211 (95%) pts who received any systemic tx, median OS (mOS) was 14.6 (95% CI: 12.2—15.4) months (mo) from the start of 1L tx. Pts having received immunotherapy had a mOS of 20.7 vs 13.9 mo (HR 0.67, 0.44—1.04; p=0.07). For 198 pts with actionable findings across TOPOGRAPH tiers, receipt of matched tx (n=37) was associated with a significantly longer mOS of 21.4 (15.0—31.8) compared with receipt of unmatched tx (n=161), mOS 12.6 mo (11.5C15.2, hazard ratio for death, HR 0.46, p<0.001). Pts with tier 1-3 actionable alterations who received matched tx had a median OS of 30.5 mo (95% CI: 18.8 - not reached, NR) compared with 12.1 mo (9.8—16.1, HR 0.39, p=0.02) if only unmatched tx received. Receipt of tier 3B/4 matched tx (n=13) only showed a trend towards longer survival, 15.6 mo vs unmatched 14.0 mo (HR 0.60, p=0.16). For 149 pts who received >1 line of systemic tx: 35 matched and 103 unmatched alone, mOS (measured from 2L tx) was 11.3 (5.7-28.4) compared with 8.3 mo (6.1-10.6) respectively (HR 0.67, p=0.10). A significantly longer OS was seen for matched vs unmatched, in pts receiving tier 1-3 tx: mOS 19.0 mo vs 8.3 mo (HR 0.43, p=0.04), but not for tier 3B/4, mOS 5.6 vs 6.7 mo HR 1.31, p=0.48. The most common genomic alterations were in TP53 (86, 39%), KRAS (59, 26%), CDKN2A (43, 19%), and ARID1A (29, 13%), while actionable findings commonly involved IDH1 (26, 12%), FGFR2 (20, 9%), ERBB2 (14, 6%), and BRAF (11, 5%). Conclusions: Receipt of genomically matched tx, particularly those supported by TOPOGRAPH tiers 1-3 evidence was associated with longer OS for pts with advanced BTC. Our results support the greater use of CGP in the management of these pts. Research Sponsor: Australian Government - Medical Research Future Fund; Omico acknowledges support from Servier and Astra Zeneca.
Efficacy and safety of first-line treatments for patients with advanced hepatocellular carcinoma: A systematic review and network meta-analysis.

Danni Li, Jingyi Li, Yunpeng Liu, Xiujuan Qu; The first hospital of China Medical University, Shenyang, China; Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, China; Department of Medical Oncology, The First Affiliated Hospital of China Medical University, Shenyang, China

Background: In recent years, the first-line treatment options for advanced HCC has been increasingly abundant, including transarterial therapies, combination of the immune checkpoint inhibitors (ICIs) and the anti-vascular endothelial growth factor (VEGF) inhibitor, ICIs combined with ICIs, and tyrosine kinase inhibitors. However, it remains to be confusing which treatment pattern would benefit people most, especially for different subgroups. Methods: A systematic literature search was conducted on PubMed, Embase, Cochrane Central Register of Controlled Trials, and American Society of Clinical Oncology and European Society of Medical Oncology meeting proceedings for III phase randomized clinical trials (RCTs) investigating first-line treatments for HCC compared with sorafenib. The survival outcomes and toxic effects of RCTs should be reported, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events (AEs) of grade 3 or higher. This systematic review was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. The random-effects model was used to calculate the summary hazard ratios (HRs) of OS and PFS. The likelihood of ORR, and AEs of grade 3 or higher was performed by odds ratios (ORs) using a random-effects model. Results: A total of 13 phase III RCTs involving 8505 patients were included in this study. Hepatic arterial infusion of oxaliplatin combined with fluorouracil (FOHAIC-1) showed OS, PFS, and ORR benefit over all other first-line therapies, except for the regimen of sorafenib plus HAIC of FOLFOX (OS: HR, 0.88; 95% CI, 0.37-2.09; ORR: OR, 1.53; 95% CI, 0.29-8.13). More importantly, we found that sorafenib combined with FOLFOX was superior to other regimens in patients with HBV infection regarding OS except FOHAIC-1 (HR, 0.57; 95% CI, 0.21-1.52) and tremelimumab-durvalumab (HR, 0.42; 95%CI, 0.16-1.11). While in HCV-infected subgroup, ICIs combined with anti-VEGF inhibitor improved OS benefit compared with tremelimumab-durvalumab (HR, 0.31; 95% CI, 0.11-0.84) and sorafenib (HR, 0.38; 95% CI, 0.16-0.88). HAIC-FO also showed significant OS benefits to other therapies in patients with portal invasion or extrahepatic metastasis. The probability of adverse events of grade 3 or higher was significantly lower with HAIC-FO than with others except for nivolumab (RR, 0.96; 95%CI, 0.51-1.82) and tislelizumab (RR, 0.57; 95%CI, 0.30-1.08). Conclusions: This network meta-analysis supports arterial infusion as the first-line treatment for patients with HCC. In portal invasion and extrahepatic metastasis subgroups, HAIC-FO may be a preferred option, with sorafenib combined with FOLFOX as an additional option in those with HBV infection. Besides, novel combination therapy should be focused on in patients with certain subgroups.

Research Sponsor: National Natural Science Foundation of China.
Phase I trial of chimeric anti-GPC3 scFv-CD3ε engineered T cells (CT0180) in patients with advanced hepatocellular carcinoma.

Yi Zheng, Qihan Fu, Qingwei Zhao, Lulu Liu, Zhou Tong, Hangyu Zhang, Peng Zhao, Weijia Fang, Xudong Zhu, Wanwan Gao, Miya Wang, Daijing Yuan, Huamao Wang, Zonghai Li, Tingbo Liang; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Clinical Pharmacy, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; CARsgen Therapeutics Ltd., Shanghai, China; CARsgen Therapeutics Ltd., Co., Shanghai, China; CARsgen Therapeutics Co., Ltd, Shanghai, China; CARsgen Therapeutics, Inc, Houston; Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Hepatocellular carcinoma (HCC) is associated with poor prognosis and high mortality. Glypican-3 (GPC3) is a heparan sulfate proteoglycan overexpressed in 70-80% of HCC and is considered a potential therapeutic target for HCC. We modified T cells with a fusion protein of anti-GPC3 single-chain fragment variable (scFv) linked to CD3ε, which incorporates into the native T cell receptor/CD3 complex forming chimeric anti-GPC3 scFv-CD3ε engineered T cells (CT0180). Preclinically, CT0180 showed competitive antitumor activity but lower cytokine release compared to 28ζ or BBζ chimeric antigen receptor T cells.

Methods: This is an open-label, dose-escalation/exploration phase I study to investigate CT0180 in patients with GPC3-positive advanced HCC (NCT04756648). The study objectives are to evaluate the safety, preliminary efficacy, and cellular pharmacokinetics of CT0180. Eligible patients underwent sequential apheresis, lymphodepletion, and cell infusion. Antiangiogenic drug monotherapy was allowed after apheresis as bridging therapy. Lymphodepletion regimen comprised fludarabine 25 mg/m² and cyclophosphamide 300 mg/m² daily for 3 days. Five dose levels (DLs, range 10^3-600 10^6 cells) with up to 3 cycles were explored using i3 + 3 design, and intra-patient dose-escalation was allowed. Data are reported as of 01-Feb-2023.

Results: From Feb-2021 to Jul-2022, 7 patients with hepatitis B virus-related HCC were treated with CT0180 (one patient each at 10^3-10^6 and 300 10^6 DL, 3 at 100 10^6 DL, and 2 at 300 10^6 DL). The median age was 46 (28–74) years. Patients had prior 2 lines or more systemic therapy, with at least one antiangiogenic tyrosine kinase inhibitor and/or anti-PD-1/PD-L1 immunotherapy. Most common grade 3-4 adverse events were hematologic toxicities, ie lymphopenia and neutropenia, which were considered to be related to lymphodepletion. No dose-limiting toxicities, immune effector cell-associated neurotoxicity syndrome, or treatment-related deaths occurred. Grade 1 cytokine release syndrome was observed in 6 patients; tocilizumab was given in one patient and no glucocorticoids were used. All 7 patients were evaluable for efficacy, in which 2 achieved partial response (PR) (30×10^6 and 300×10^6 DL) and 3 achieved stable disease (SD) (10×10^6, 100×10^6 and 300×10^6 DL). One patient sustained PR for 6.7 months, and one patient sustained SD for 6.1 months with follow-up ongoing. Median follow-up time was 15.9 months, and median overall survival was 11.6 months with 3 patients alive at last follow-up. CT0180 transgene copy number ranged 47–4487 copies/μg genomic DNA and peaked on either D3 or D7. Interleukin-6 increased and peaked on D1 after CT0180 infusion in most patients.

Conclusions: CT0180 demonstrated manageable safety profile and promising antitumor potential. Further exploration of CT0180 in HCC is needed. Clinical trial information: NCT04756648. Research Sponsor: CARsgen Therapeutics Ltd.
A prospective, open-label, randomized, controlled trial of radiofrequency ablation versus stereotactic body radiation therapy for recurrent small hepatocellular carcinoma.

Yaojun Zhang, Mian Xi, Minshan Chen, Li Xu, Shi-Liang Liu, Mengzhong Liu, Collaborative Innovation Center for Cancer Medicine, State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center; Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Effective treatments are urgently needed to improve the prognosis of patients with recurrent hepatocellular carcinoma (HCC). Previous studies demonstrated that both radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) were promising therapies for recurrent small HCC. This trial was designed to compare the efficacy and safety of RFA versus SBRT in patients with recurrent small HCC. Methods: This is a prospective, open label, randomized controlled trial, in which patients aged between 18 and 75 years with recurrent small HCC (occurred more than 3 months after hepatectomy or RFA, a solitary HCC ≤ 5.0 cm in diameter without vascular invasion or extrahepatic metastasis), KPS score ≥ 90, Child-Pugh score ≤ 6, adequate organ function, and estimated life expectancy ≥ 6 months were considered eligible. All patients were assigned 1:1 to RFA or SBRT group, and stratification was performed according to tumor size (< 2.0 cm or 2.1-5.0 cm). The primary endpoint was 2-year local progression-free survival. Secondary endpoints were progression-free survival, locoregional control, overall survival, and safety. Results: A total of 170 patients were recruited during August 2019 to May 2022 (83 in RFA arm and 87 in SBRT arm). In the ITT population, median age was 56 (range, 33-75) and 15 were female. Baseline characteristics were well balanced between treatment arms. Adverse events occurred in RFA and SBRT were mainly grade 1 or grade 2 in severity, and were gastrointestinal and constitutional symptoms, or abnormal laboratory investigations. The most common adverse events were bilirubin increase (14.6%) and AST increase (13.3%) in RFA group vs ALT increase (20.0%) and AST increase (15.3%) in SBRT group. No Grade 3-4 adverse events or mortality were noted. Late adverse events were hardly observed after 3 months. The follow-up of survival data is ongoing. Conclusions: Both RFA and SBRT are tolerable and safe for patients with recurrent small HCC. This randomized controlled trial will report the survival outcomes in 2024, which will make an important contribution in clinical decision-making for recurrent small HCC. Clinical trial information: NCT04047173. Research Sponsor: None.
Circulating tumor DNA (ctDNA) analyses in patients with HER2-positive biliary tract cancer (BTC) treated with trastuzumab deruxtecan (T-DXd): Exploratory results from the HERB trial.

Akihiro Ohba, Chigusa Morizane, Yasuyuki Kawamoto, Yoshito Komatsu, Makoto Ueno, Satoshi Kobayashi, Masafumi Ikeda, Mitsuhito Sasaki, Junji Furuse, Naohiro Okano, Nobuyoshi Hiraoka, Hiroshi Yoshida, Aya Kuchiba, Ryo Sadachi, Kenichi Nakamura, Naoko Matsui, Yoshiaki Nakamura, Wataru Okamoto, Takayuki Yoshino, Takui Okusaka; National Cancer Center Hospital, Tokyo, Japan; Hokkaido University Hospital, Sapporo, Japan; Kanagawa Cancer Center, Yokohama, Japan; National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center Hospital East, Kashiwa, Chiba, Japan; Kyorin University Faculty of Medicine, Tokyo, Japan; Hiroshima University Hospital, Hiroshima, Japan; Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: In the phase 2 HERB trial (NCCH1805; JMA-IIA00423), T-DXd exhibited promising activity among patients with HER2-positive BTC (ASCO 2022 ab 4006). HER2 positivity was defined as tumor tissue immunohistochemistry (IHC) 3+ or IHC 2+ with in situ hybridization (ISH) positivity. HER2 gene amplification (HER2-amp) can also be detected in ctDNA, which may be an alternative when tumor tissue is not available. ctDNA may also detect tumor molecular changes during treatment and at disease progression.

Methods: In this ancillary study, we collected plasma samples for ctDNA analysis (Guardant360) at baseline (BL), day 1 of cycle 2 (C2D1; ie, day 22 of treatment), and end of treatment (EOT). The relationships between clinical outcomes and ctDNA genomic profiles were evaluated. Results: Among the 30 patients in the full analysis set of HERB (22 with HER2-positive and 8 with HER2-low BTC), plasma samples for ctDNA were obtained from 30, 29, and 24 at BL, C2D1, and EOT, respectively. HER2-amp was found in ctDNA of 8 BL samples, all of which were from tissue HER2-positive patients. This included 50% (5 of 10) of the IHC 3+ tumors and 25% (3 of 12) of the IHC 2+/ISH + tumors. Comparing clinical outcomes for patients with HER2-amp in ctDNA (n=8) to those with HER2-positive in tissue (n=22), the confirmed objective response rate (cORR) was 50.0% (95% CI, 15.7–84.3), including all 2 CR cases, vs 36.4% (95% CI, 17.2–59.3); median duration of response was 7.9 (95% CI, 2.8–11.5) vs 7.4 months (95% CI, 2.8–NA), median progression-free survival (PFS) was 6.1 (95% CI, 2.8–20.3) vs 5.1 months (95% CI, 3.0–7.3), and median overall survival was 10.8 (95% CI, 4.7–NA) vs 7.1 months (95% CI, 4.7–14.6). Plasma copy number (median 5.1, range 2.3–9.9) was not associated with response or survival, even after adjusting for maximum variant allele frequency (MAF). Common BL genomic mutations found in ctDNA were in TP53 (n=19, 63%), PIK3CA (n=8, 27%), and TERT (n=7, 23%). No mutation was associated with treatment efficacy. Median MAF decreased from 7.3% at BL to 1.6% at C2D1. Decreased MAF was associated with better response (CR, PR, and SD) and longer PFS. Among 24 EOT samples, including 7 from patients with BL HER2-amp in ctDNA, 10 (42%) acquired potential resistance alterations, most related to receptor tyrosine kinase, MAPK, and PI3K pathways. HER2-amp was lost at EOT in 4 of the 7 patients with HER2-amp detected in BL ctDNA. Conclusions: Using a ctDNA assay, HER2-amp was detected in 36% of patients with tissue HER2-positive BTC. Those with HER2-amp in ctDNA than HER2-positive in tissue had potentially higher cORR and longer survival with TDXd. Clinical trial information: JMA-IIA00423. Research Sponsor: Japan Agency for Medical Research and Development; Daiichi Sankyo.
BOLD-100-001 (TRIO039): A phase 1b/2a study of BOLD-100 in combination with FOLFOX chemotherapy in patients with pre-treated advanced gastric and biliary tract cancer: Efficacy and safety analysis.

Grainne M. O’Kane, Jennifer L. Spratlin, Do-Youh Oh, Sun Young Rha, Elena Elimova, Petr Kavan, Moon Ki Choi, Rachel Anne Goodwin, Seung Tae Kim, Dong-Hoe Koo, Khalif Halani, E Russell McAllister, Michelle Jones, Malcolm Snow, Yasmin Lemmerick, Gonzalo Spera, Jim Pankovich; Trinity St. James’s Cancer Institute, Dublin, Ireland; Cross Cancer Inst, Edmonton, AB, Canada; Seoul National University Hospital, Seoul, Korea, Republic of (South); Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Jewish General Hospital, Montréal, QC, Canada; National Cancer Center, Goyang-Si, South Korea; The Ottawa Hospital Research Institute, Ottawa, ON, Canada; Samsung Medical Center, Seoul, South Korea; Kangbuk Samsung Hospital, Seoul, South Korea; Emes, Vancouver, BC, Canada; Bold Therapeutics Inc., Vancouver, BC, Canada; Bold Therapeutics, Inc., Vancouver, BC, Canada; Translational Research in Oncology, Canada, Edmonton, AB, Canada; Translational Research in Oncology, Montevideo, Uruguay

Background: BOLD-100 is a first-in-class ruthenium-based anticancer agent in Phase 1b /2a clinical development for the treatment of advanced gastrointestinal (GI) cancers in combination with FOLFOX. BOLD-100 demonstrated synergy in established preclinical models in combination with various anticancer therapies, particularly in resistant cell lines. Methods: This is a prospective, Phase 1b/2a study of BOLD-100 in combination with FOLFOX for the treatment of gastrointestinal cancers including biliary tract (BTC) and gastric (GC) cancers. Patients are administered BOLD-100+FOLFOX on day 1 of each 14-day cycle. Four cohorts are treated at the BOLD-100 RP2D of 625 mg/m2 with FOLFOX until progressive disease or unacceptable toxicity. BTC and GC pt cohort data are presented. The primary objective is to evaluate the efficacy of BOLD-100 in three clinical endpoints (PFS, OS, and ORR). Disease Control Rates (DCR) for each cohort are also determined. Bayesian modelling is used to continually reassess these endpoints, the posterior probability of superiority to an historical landmark for each endpoint. Results: As of 31Dec22, 22 pts with advanced metastatic BTC and 13 pts with advanced GC median age 61 in each cohort were treated. The BTC pts received a median of 2 prior systemic therapies while the GC patients had a median of 3. All patients presented with stage IV disease. 21/22 BTC patients received prior GEM/CIS and while on study a median of 4 cycles BOLD-100+FOLFOX [range 1-19]. Median PFS was 5.0 [3.1, 8.9] months, median OS 7.3 [4.2, 14] months, ORR 6% [1,23] and DCR 83% [62, 95] in 18 evaluable patients. Four pts remain on treatment and 3 in follow-up. 10/13 GC pts were previously treated with a platinum; currently there are 9 evaluable patients. To the data cut-off, patients received a median of 6 cycles BOLD-100+FOLFOX [1-16]. Median PFS was 5.5 [2.8, 13] months and median OS 15 [5.4, 63] months. Two pts achieved a partial response and 6 pts had stable disease for an overall DCR of 89% (8/9 [59%,99%]). Five pts remain on treatment with an additional 6 in follow-up. Study treatment was well tolerated. For the 35 treated patients, 33 reported 1 or more treatment-emergent adverse events (AEs), most commonly neutrophil count decreased (n = 15, 43%), nausea (n = 12, 34%), fatigue (n = 10, 29%), and anemia (n = 10, 29%). Most of the AEs were grade (G) 1-2. 14 patients (40%) reported G3/4 neutrophil count decreased. Conclusions: BOLD-100 plus FOLFOX is an active and well-tolerated treatment regimen in the heavily pre-treated Stage IV biliary tract and gastric cancer study populations. There were no new safety signals. The preliminary mPFS, mOS, ORR and DCR data in this interim analysis demonstrate significant improvement over the currently available therapies for these difficult to treat advanced GI cancers. Clinical trial information: NCT04421820. Research Sponsor: Bold Therapeutics Inc.
A phase II study of olaparib and durvalumab in patients with IDH-mutated cholangiocarcinoma.

Erica S. Tsang, Grainne M. O’Kane, Jennifer J. Knox, Eric X Chen; Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: IDH1/2 mutations (m) occur in approximately 25% of cholangiocarcinomas (CCAs) (20% intrahepatic, < 5% extrahepatic) and result in the accumulation of R-2-hydroxyglutarate (R2HG). R2HG suppresses homologous recombination repair and as a result IDH1/2m are hypothesized to predict PARP inhibitor sensitivity. PARP inhibition upregulates PD-L1 and the combination is thought to be synergistic. We conducted a phase II trial of olaparib with durvalumab for patients with IDH-mutated cholangiocarcinoma. Methods: Patients with advanced IDHm CCA were enrolled in this phase II open-label study (NCT03991832). Patients received olaparib 300 mg twice daily continuously and durvalumab 1500 mg IV every 4 weeks. Simon’s optimal two-stage design was used, with an interim analysis planned for efficacy. 10 patients were accrued in the first stage, with a plan for expansion if ≥2 responses were observed. The primary objective was to determine the overall response rate (RECIST 1.1) and disease control rate (DCR). Secondary objectives included progression-free survival, overall survival, and safety of the olaparib and durvalumab combination. Results: 10 patients with IDH1m were enrolled in this study between January 2020-August 2021. Median age was 63.5 years (range 49-78), and 50% were female. All patients had a baseline ECOG PS of 0-1. 40% of patients had prior surgical resections and subsequently developed recurrent disease. 20% of patients had ≥2 lines of prior chemotherapy, with 90% receiving prior platinum. Median duration of treatment was 1.95 months (range 1.8-13.5). There were no treatment-related grade 3-4 toxicities. Any grade toxicities included fatigue (100%), nausea (60%), anemia (20%), hypothyroidism (20%), elevated liver enzymes (20%). We did not observe any complete or partial responses. The DCR was 30% with 3 patients demonstrating stable disease. One patient remained on treatment for 13.5 months, and was eventually taken off study due to clinical progression. The median PFS was 1.97 months (95% CI 1.73-3.93). Given that no responses were seen in the initial 10 patients, the study did not proceed to Stage 2. Conclusions: While the combination of olaparib and durvalumab was well-tolerated, this study was discontinued after Stage I due to lack of efficacy. IDH1/2m may not induce a BRCAness phenotype and further correlative studies are planned to evaluate this. Clinical trial information: NCT03991832. Research Sponsor: AstraZeneca.
Racial and socioeconomic disparities in time to chemotherapy and survival in patients with pancreatic cancer.

Shivani Shah, James Rock, Rodney E. Wegner, Dulabh K. Monga; Allegheny General Hospital, Pittsburgh, PA; Division of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA; Division of Medical Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA

Background: Pancreatic cancer is traditionally known to be an aggressive malignancy, requiring timely diagnosis and treatment, including chemotherapy and/or surgery. Prior studies have evaluated variances in overall survival (OS) based on race or income; however, research regarding time to treatment based on racial and socioeconomic disparities is underwhelmingly studied. Our project sought to evaluate the impact of race and income on time to chemotherapy and OS in pancreatic cancer patients receiving neoadjuvant or adjuvant chemotherapy.

Methods: The National Cancer Database (NCDB) from 2004-2020 was reviewed for patients with a diagnosis of pancreatic cancer, including all types and stages. Exclusion criteria included: no documented income level, time to first treatment surgery, or time to chemotherapy. Our patient population was then separated into two cohorts: neoadjuvant and adjuvant. Income level was stratified into the following: < $30,000, $30,000-34,999, $35,000-$45,999, and > $46,000. Race was also noted. We utilized a logistic regression to identify factors associated with longer time to chemotherapy (using median time to chemotherapy as a benchmark for early or later initiation of chemotherapy). A Cox proportional hazards model was used to identify factors associated with worse survival. A p-value < 0.05 was deemed significant.

Results: Our final sample size included 64,640 patients. 6,887 (10.6%) of patients had an income less than $30,000. 55,340 (85.6%) of patients were Caucasian, 6,379 (9.9%) patients were African American, and 172 (0.002%) were American Indian. 18,679 (28.9%) received neoadjuvant chemotherapy, and 45,961 (71.1%) received adjuvant chemotherapy. Median time to chemotherapy was 27 [0-2048] days and 71 [0-1895] days in the neoadjuvant and adjuvant cohorts, respectively. Within both cohorts, income > $46,000 was noted to have significantly earlier time to chemotherapy compared to lower income levels. Those privately insured had significantly earlier time to chemotherapy compared to uninsured. The African American population was associated with a later time to first chemotherapy in comparison to Caucasians in both subgroups. A significantly less OS in the African American population was appreciated in the neoadjuvant cohort (HR 0.92, p-value 0.02), but not the adjuvant cohort.

Conclusions: Our retrospective analysis emphasizes that minorities and/or those with a poor socioeconomic status have significant delay in time to chemotherapy in the neoadjuvant and adjuvant setting. Within the African American neoadjuvant cohort, a significantly worse OS was highlighted. This study emphasizes racial and socioeconomic disparities in our healthcare system. Limitations of our study include its retrospective nature and no information regarding the type of surgery the patients received, which could further account for differences in time to chemotherapy. Research Sponsor: None.
Progression-free survival as a surrogate endpoint of overall survival in advanced biliary tract cancer: A meta-analysis of randomized trials and individual-patient level correlation.

Carles Fabregat Franco, Florian Castet, Adelaida La Casta, Jorge Adeva, Alfredo Castillo, Andrés Muñoz, Paloma Peinado, Eva Martínez de Castro, Miriam Lobo, Monica Granja, Rosa María Rodriguez-Alonso, Ana Fernández Montes, Ruth Vera, Javier Gallego, Begoña Graña, Ismael Ghanem, Inmaculada Álés, Raquel Molina, Teresa Macarulla, Enrique Aranda, The Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD); Gastrointestinal and Endocrine Tumor Unit, Vall d’Hebron Institute of Oncology (VHI0), Hospital Universitari Vall d’Hebron, Vall d’Hebron Barcelona Hospital Campus, Barcelona, Spain; Department of Medical Oncology UGC Oncología Guipúzcoa, País Vasco, Spain; Department of Medical Oncology Hospital 12 de Octubre, Madrid, Spain; Department of Medical Oncology Hospital Universitario Central de Asturias, Asturias, Spain; Department of Medical Oncology Hospital Universitario Gregorio Marañón, Madrid, Spain; Department of Medical Oncology Centro Integral Oncológico Clara Campal, HM Hospitales, Madrid, Spain; Department of Medical Oncology University Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain; Department of Medical Oncology Consorcio Hospital General Universitario de Valencia, Valencia, Spain; Department of Medical Oncology, Hospital Clínico San Carlos. Instituto de Investigación Hospital Clínico San Carlos (IdISSC), University Complutense, Madrid, Spain; Department of Medical Oncology IMIBIC, Universidad de Córdoba, CIBERONC, Instituto de Salud Carlos III. Hospital Universitario Reina Sofía, Córdoba, Spain; Department of Medical Oncology Complejo Hospitalario Universitario de Ourense, Ourense, Spain; Department of Medical Oncology, University Hospital of Navarra, Instituto de Investigación Sanitaria de Navarra, IdISNA, Navarra, Spain; Department of Medical Oncology Hospital General Universitario de Elche, Alicante, Spain; Department of Medical Oncology Complejo Hospitalario Universitario A Coruña. Instituto Investigación Biomédica INIBIC, A Coruña, Spain; Department of Medical Oncology Hospital Universitario La Paz, Madrid, Spain; Department of Medical Oncology H. Universitario Regional y Virgen de la Victoria, Málaga, Spain; Department of Medical Oncology Hospital Universitario Príncipe de Asturias, Madrid, Spain

Background: Biliary tract cancer (BTC) is a heterogeneous group of diseases commonly diagnosed at advanced stages. Overall survival (OS) is the gold-standard primary endpoint in randomized controlled trials (RCT). However, the increasing use of subsequent lines of therapies and cross-over designs may confound the treatment effect. We therefore explored the use of progression free survival (PFS) as a surrogate endpoint of OS both at the trial-level and at the patient-level. Methods: For the trial-level correlation, we conducted a systematic review of RCTs in advanced BTC following the PRISMA guidelines. We searched PubMed, the Cochrane Central Register of Controlled Trials and Clinical-Trials.gov from database inception to June 2022 and identified all randomized phase II/III trials testing systemic therapies for advanced BTC. We used a weighted linear regression to measure the correlation of log-transformed hazard ratios (HR) of OS and PFS based on trial size and calculated the surrogate threshold effect (STE). We used the IQWiG framework to define the strength of evidence. For the individual-level analysis, we included patients with advanced BTC treated with first and second line chemotherapy in the real-world RETUD registry. We estimated the correlation via the iterative multiple imputation method. Results: From a total of 1992 studies, we identified 32 RCTs including 70 treatment arms and 5140 patients that fulfilled the inclusion criteria. Twenty-three trials were performed in the first line setting and most were phase II RCTs (N = 23). We found a moderate correlation between OS and PFS (R = 0.79, 95% CI 0.61-0.89). The slope of the regression line was 0.62±0.08, indicating that a 10% risk reduction in PFS will result in a 6.2%±0.8% improvement in OS. The STE was 0.69, suggesting that in a hypothetical trial of 400 patients, a PFS HR of 0.69 will likely result in a significant improvement on OS. Regarding the individual-level correlation, a total of 593 patients with advanced BTC were included. The median age of patients was 68y (IQR 59-74), most were males (54%) and received platinum-based chemotherapy (73.1%). In the first line setting, the median OS was 9.7 months (95% CI 8.7-10.5) and median PFS was 5 months (95% CI 4.5-5.5). We observed a strong correlation between PFS and OS (r = 0.84, 95% CI 0.81-0.86). In the second line setting (N = 259), a similar correlation was observed to the first-line setting (r = 0.76, 95% CI 0.72-0.8). Conclusions: At the trial-level, in this analysis treatment effects on PFS were moderately correlated with OS. A HR < 0.69 in PFS suggested that it would likely lead to a significant OS benefit in a hypothetical trial including 400 patients. At the individual-level, PFS and OS were strongly correlated in a real-world cohort. Future validation in patients treated in the context of randomized trials is warranted. Research Sponsor: None.
Ex-vivo analysis of programmed cell death on fibrolamellar carcinoma.

Olutani-Grace Ajay, Paul Kent, Robert Alan Nagourney, Tom Stockwell, Jessica Ellison, Susanne M. Swasey, Jordan C Tasse, Erik Schadde, Abhinav Humar, Tom Kato, Darrell Yamashiro; Rush University Medical School, Chicago, IL; FibroFighters Foundation, River Forest, IL; Nagourney Cancer Institute, Long Beach, CA; FibroFighters.org, Temecula, CA; Rush University Medical Center, Chicago, IL; University of Zürich, Zurich, Switzerland; upmc, Pittsburgh, OH; NY Presbyterian, New York, NY; Columbia University Medical Center, New York, NY

Background: Fibrolamellar carcinoma (FLC) is a rare liver cancer with surgery as the only established treatment. Relapse is common (>80%) and with 40% unresectable, there is a need for rationale systemic therapy. Empiric combinations, especially with lenvatinib (LEN) and gemcitabine (GEM), show promise, but are lacking a CLIA licensed laboratory rationale. Ex-Vivo Analysis of Programmed Cell Death (EVA-PCD), from Nagourney Cancer Institute, is an attempt to meet this need. Methods: Nagourney Institute analyzed FLC tissue (as previously described), with a panel of 34 single/26 combinations of available/promising agents from 18 drug classes. Drug concentration with 50% cell death (LC50), below, within, or above 1-standard deviation of the mean (n ≥ 15), define Highly-Sensitive/Intermediate/Resistant, respectively. Active/Moderate/Inactive are similarly defined but with n < 15. Actionable defines clinically available drug(s), not resistant/inactive and ≥ 6 assays. Results: Forty-four samples from 40 patients (17M,23F, age 6-56, 23 states/4 countries) were analyzed: 80% were viable and 69% of high quality for a total of 378 assays (avg 12/patient). However, all patients had actionable agents, and 78% of the assays showed activity in at least some patients. All the universally resistant/inactive assays (22%) were single agent. 76% of assays were actionable in at least one patient (100% for combinations compared to 62% for single agents). EVA-PCD replicate FLC studies and experience, such as the failure of monotherapy and the importance of LEN. Of 11 patients who had treatment that matched testing, 72% responded as predicted, including 6 with 100% response to LEN and/or QUE as predicted. Overall LEN/QUE, LEN/EVE, TRE, REG, QUE, 5FU/INF performed the best, while single agent ALP, CAB, LAR, VOR, GEM, DAS and IBR all showed 0% activity when tested 5 times. The largest challenge is the need for an adequate amount of viable tissue to arrive within 24 hours. However our experience demonstrates that it is feasible from other countries and across the US. Conclusions: This is the first demonstration of CLIA approved human FLC tumor testing. Data are in line with literature and correlates clinically. Prospective data are needed to fully incorporate EVA-PCD testing into the clinic. Research Sponsor: None.
Background: Gut microbiota established crucial roles in host metabolism and several diseases, particularly cancers. Distinct bacterial profiles from intestine are found to be a potential factor in carcinogenesis, while some of those are associated with detrimental treatment to the responsiveness in various types of cancer. Association of gut microbiota and treatment outcome has been thoroughly investigated in intrahepatic cholangiocarcinoma (ICCA). The present study aimed to compare gut microbiota profiles between chemotherapy responder and non-responder in ICCA patients.

Methods: Unresectable or metastatic ICCA patients were recruited in the study. The criteria of all patients were naïve to chemotherapy. All patients received first line combination of cisplatin 25 mg/m² and gemcitabine 1000 mg/m² at day1 and day 8 in every 21-day cycle and were given up to 8 cycles. The primary endpoint was to evaluate the association between gut microbiota and the objective response rate. Bacterial genomic DNA samples were extracted from the stool using a commercial genomic DNA isolation kit (Qiagen, Hilden, Germany) and then underwent next-generation sequencing. Data analyses were conducted by using QIIME2 and Analysis of Compositions of Microbiomes with Bias Correction (ANCOM-BC).

Results: Seventeen ICCA patients were recruited. The objective response rate was 23.5% comparable to historical study. Chemotherapy responder group was defined as partial response patients (N = 4) and chemotherapy non-responder group included stable of disease and progressive disease (N = 13). Baseline characteristics were similar including age, sex, ECOG performance status, numbers of metastatic organ and CA 19-9 in two groups. Median Age were 63 years old (60-70) and 61 (45-73), respectively. Alpha-diversity and beta-diversity were not different between two groups. In chemotherapy non-responder group, some taxa were dominantly observed including Ruminococcaceae, Orbibacterium, Oxalobacter, Peptostreptococcus, Aggregabacter, which had been previously reported increasing in ICCA patients. Interestingly, Ruminococcaceae, which was previously documented to be correlated with vascular invasion, was significantly increased abundance in non-responder group. Moreover, the median progression-free survival (PFS) was improved in chemotherapy responder group compared to non-responder group 11.8 and 6.6 month, respectively. Large sample sizes study to confirm this study result should be developed.

Conclusions: Distinct bacteria from gut microbiota such as Ruminococcaceae has inversely associated with chemotherapy response in ICCA patients receiving first line cisplatin and gemcitabine combination, suggesting the possibility of the poorer PFS. Research Sponsor: Faculty of Medicine, Chiang Mai University.
Real-world multicentre analysis of patients with hepatocellular carcinoma (HCC) treated with atezolizumab and bevacizumab (A+B): Efficacy, esophagogastroduodenoscopy (EGD) uptake and bleeding complications.

Cha Len LEE, Mark Freeman, Conor O'Donnell, Gordon Taylor Moffat, Ekaterina Kosyachkova, Hanna Lyubetska, Brandon M. Meyers, Valerrie Lynn Gordon, Philip Q. Ding, Aileigh Kay, Roxana Bucur, Winson Y. Cheung, Jennifer J. Knox, Vincent C. Tam; Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; CancerCare Manitoba, Winnipeg, MB, Canada

Background: The IMbrave150 trial established A+B as a standard of care for HCC and an EGD within 6 months (mos) of starting treatment to detect esophageagastroduodenal varices and prevent bleeding complications was advised. However, the value of performing EGD in all patients (pts) is unknown.

Methods: We conducted a retrospective analysis of all HCC pts treated with A+B between July 2020 to August 2022 at 5 cancer centres from the Canadian provinces of Ontario, Alberta and Manitoba (members of the HCC-CHORD Consortium). Pts characteristics and treatment history including efficacy, EGD details and bleeding events were collected. Overall survival (OS), progression-free survival (PFS) and response rate (RR) were calculated. A comparative analysis was conducted to compare the correlation between the EGD uptake and bleeding events. Results: A total of 112 pts were identified (median age 66 years, 87% male, 24% East Asian, 67% liver cirrhosis, 33% HCV, 25% HBV, 15% NASH, 23% BCLC B, 71% BCLC C, 91% Child-Pugh A, 29% main portal vein invasion, 45% ALBI grade 1 and 54% ALBI grade 2). Prior to systemic, 61% had locoregional therapies. 90% received A+B as first-line therapy, while 9% received it as second-line and 1% as third-line. Outcomes of pts treated with A+B are shown. Before starting A+B, 78 pts (70%) had completed an EGD within 6 mos. Of these, 32 pts (41%) had evidence of varices on EGD, and 15 (20%) required treatment with either banding or beta-blockers. All bleeding events in this population was 15% (n=17). Bleeding rates in the EGD and non-EGD groups were 18% (n=14) and 9% (n=3), respectively. Bleeding adverse events were 5%(n=6) gastrointestinal vs 10%(n=11) non-gastrointestinal (6 epistaxis, 1 ecchymosis, 1 periodontal and 3 unspecified). The GI bleeding rates in the EGD and non-EGD groups were 6% (n=5) and 3% (n=1). Conclusions: Outcomes of HCC pts treated with A+B in Canada are comparable to those observed in the IMbrave150 trial. Our study detected and treated varices at twice the rate of the IMbrave150 trial among the EGD group, reflecting real-world treatment of a high-risk population. Yet, pts who had no EGD before starting A+B, presumably due to a low risk of portal hypertension based on physicians’ judgement, did not experience more bleeding/GI bleeding than those who had an EGD. This supports the approach of selective EGD prior to A+B, and more guidelines are needed in this area. Outcomes and response rate of patients treated with Atezolizumab with Bevacizumab in this study. Research Sponsor: None.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), mos</td>
<td>20.3 (16.5-NR)</td>
</tr>
<tr>
<td>Pts with bleeding</td>
<td>20.3 (13.0-NR)</td>
</tr>
<tr>
<td>Pts without bleeding</td>
<td>19.7 (16.5-NR) (p=0.78)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mos</td>
<td>9.6 (5.1-11.9)</td>
</tr>
<tr>
<td>Median follow-up time, mos</td>
<td>10.4 (4.4-47.6)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1%</td>
</tr>
<tr>
<td>Partial response</td>
<td>35%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>41%</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>23%</td>
</tr>
</tbody>
</table>
Association of a high E2F targets score with survival in hepatocellular carcinoma patients.

Kohei Chida, Masanori Oshi, Arya Mariam Roy, Takaumi Yachi, Masaki Nara, Kyogo Yamada, Osanu Matsuura, Tatashi Hashizume, Itaru Endo, Kazuaki Takabe; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Mutsu General Hospital, Mutsu, Japan; Yokohama City University Graduate School of Medicine, Yokohama, Japan

**Background:** Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality. Multiple staging systems have all been proposed to date; however, the optimal tool for stratification of prognosis is still not universally accepted. E2F targets are the essential component of cell proliferation, thus we hypothesized that a score to quantify E2F activity is expected to reflect the aggressiveness and prognosis of HCC. **Methods:** Total of 655 HCC patients from TCGA (The Cancer Genome Atlas) -HCC (n=358), GSE6764 (n=75), GSE76427 (n= 115), and GSE89377 (n=107) cohorts were analyzed. The score was generated using MSigDb Hallmark E2F Targets gene set using Gene Set Variation Analysis. **Results:** The E2F targets scores of TGCA-HCC patients showed a bimodal distribution, thus high vs. low score groups were divided by median. As expected, high E2F targets enriched all of the Hallmark cell proliferation-related gene sets; E2F targets, G2M checkpoint, MYC targets v1 and v2, and Mitotic spindle. It also enriched gene sets known to aggravate cancer, such as Glycolysis, mTORC1 signaling, DNA repair, and Unfolded protein response. E2F targets were significantly associated with histological grade, tumor size, and stage, as well as proliferation score and MKI67 expression. Furthermore, a higher E2F targets score was significantly associated with higher intra-tumoral genomic heterogeneity and homologous recombination deficiency, suggesting greater tumor aggressiveness. In agreement, E2F targets score correlated with the pathological progression from normal liver, cirrhosis, dysplasia, to early and advanced HCC consistently in two cohorts (GSE6764 and GSE89377). Further, the abundance of hepatocytes, fibroblasts, adipocytes, and lymphatic endothelial cells were all significantly less in high E2F HCC, which reflects proliferative cancer. On the other hand, there was no relationship between E2F and mutation rates or neoantigens. High E2F was associated with high infiltration of anti-cancerous immune cells; CD8, CD4 memory, and Th1 cells, however, there was no difference in cytolytic activity, and it did not enrich any of immune response-related gene sets. High E2F HCC was associated with worse disease-free (DFS), disease-specific (DSS), and overall survival (OS), and this was the case in both early (I and II) and late (III and IV) stages. A multivariate analysis revealed that the E2F targets score was an independent prognostic factor for OS (HR=1.68, 95%CI= 1.15–2.46, \( p = 0.007 \)) as well as DSS (HR=1.81, 95%CI=1.27–2.59, \( p = 0.001 \)) in patients with HCC. **Conclusions:** We found that the E2F targets score not only indicates cell proliferation, but also is associated with cancer aggressiveness and worse survival. Our findings suggest a possible future use of the E2F targets score as a prognostic biomarker in patients with HCC. Research Sponsor: U.S. National Institutes of Health; Mutsu Rotary Club; U.S. National Institutes of Health; Department of Defense BCRP grants; Roswell Park Comprehensive Cancer Center.
Application of the albumin-bilirubin (ALBI) grade as predictive marker of atezolizumab plus bevacizumab (A+B) treatment outcomes for patients with advanced hepatocellular carcinoma (HCC): Real-world retrospective analysis at Veterans Health Administration (VHA).

Munaf Alkadimi, Maria Elena Fierro, Lauren Diaz Boyle, Kana Lucero, Kathleen Franklin, Michael Mader, Zohra Nooruddin; University of Texas Health Science Center at San Antonio, San Antonio, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; The University of Texas Health Science Center-San Antonio, San Antonio, TX; South Texas Veterans Health Care System, San Antonio, TX; Audie L. Murphy Memorial Veterans Hospital, San Antonio, TX; University of Texas Health San Antonio, San Antonio, TX

Background: Most clinical trials use Child-Pugh (CP) for patient selection; this subjective scale was originally developed to assess liver function in cirrhosis, thus cannot be applied to HCC patients with non-cirrhotic background. Alternatively, ALBI grade is an objective and validated prognostic system that has demonstrated improved accuracy to predict survival and liver function decline in HCC patients. Our real-world study aims to assess the ALBI grade as a predictive marker of treatment response in patients with advanced HCC who received (A+B) within the VHA. Methods: VHA patients with HCC receiving 1st line therapy with A+B were identified through EMR using ICD-9 or ICD-10 codes between 1 Jan 2007 and 31 Dec 2021. Patients were followed from their A+B initiation date through the earliest of the last VHA visit, loss to follow up, death, or end of study on Jan 31, 2023. Structured electronic health record and chart review data were retrospectively collected to determine patient baseline characteristics, treatment response, overall survival (OS), and progression-free survival. Survival rates were based on patients with at least 6 months or 1 year of time (as indicated) from A+B initiation until the chart was reviewed; patients without a scan or known date of scan were excluded from PFS calculations. The Chi-Squared test was used to compare rates. Results: 332 patients were included in the study. The median age was 67 yrs, 99% were males, 63% non-Hispanic White, 26% Black, 86% with ECOG < 1, 84% had CPS class A, 16% had CPS class B and C, 56% had viral hepatitis-caused HCC, 20% had no cirrhosis present, and 60% had prior local therapies. There was a statistically significant difference in progression free survival (PFS) and over survival (OS) amongst different ALBI grades as shown. Conclusions: In our retrospective cohort, it was clear that patients with ALBI grade 1 had improved PFS and OS compared to ALBI score grade 3. Patients with ALBI score grade 2 also had a moderate response to treatment with modest OS and PFS compared to patients with ALBI score grade 3. Utilizing stratification ability ALBI grade in future clinical trials may improve prognostic power facilitating ideal patient selection. Research Sponsor: None.

End points for VA HCC patients given AB as 1st line, with breakdown by ALBI grade at staging.

<table>
<thead>
<tr>
<th>Characteristic of Interest</th>
<th>ALBI grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>97 (29.2%)</td>
<td>207 (62.3%)</td>
<td>28 (8.4%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>OS: 6 mo</td>
<td>84 (86.6%)</td>
<td>150 (72.5%)</td>
<td>9 (32.1%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>OS: 1 yr</td>
<td>61 (70.9%)</td>
<td>93 (48.2%)</td>
<td>4 (16.0%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Objective Response Rate (CR + PR)</td>
<td>29 (30.8%)</td>
<td>62 (30.7%)</td>
<td>5 (20.9%)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Disease Control Rate (CR + PR + SD)</td>
<td>61 (64.8%)</td>
<td>123 (60.9%)</td>
<td>12 (50.0%)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>PFS: 6 mo</td>
<td>62 (66.0%)</td>
<td>118 (59.0%)</td>
<td>7 (29.2%)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>PFS: 1 yr</td>
<td>41 (48.8%)</td>
<td>61 (33.2%)</td>
<td>3 (14.3%)</td>
<td>0.004</td>
<td></td>
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</tbody>
</table>

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Comprehensive profiling of clock genes expression in hepatocellular carcinoma (HCC).

Francesca Battaglin, Yasmine Baca, Joanne Xiu, Shivani Soni, Sandra Algaze, Priya Jayachandran, Eavanthe T. Roussos Torres, Shannon M. Mumenthaler, Jae Ho Lo, Pooja Mittal, Wu Zhang, Richard M. Goldberg, Benjamin Adam Weinberg, Emil Lou, Anthony F. Shields, John Marshall, Sanjay Goel, Anthony B. El-Khoueiry, Steve A. Kay, Heinz-Josef Lenz; Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Caris Life Sciences, Phoenix, AZ; Lawrence J. Ellison Institute for Transformative Medicine; Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; West Virginia University Cancer Institute and the Mary Babb Randolph Cancer Center, Morgantown, WV; Ruesch Center for The Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; University of Minnesota, Minneapolis, MN; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Ruesch Center for The Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: The circadian clock mechanism controls the physiological homeostasis of the liver and plays a key role in hepatocarcinogenesis. Recent evidence unveiled core clock proteins as novel therapeutic targets in cancer. Our group showed that clock regulators BMAL1 and CLOCK can promote proliferation of liver cancer cells by modulating the cell cycle checkpoint kinase Wee1. Here we further evaluated the molecular landscape of clock pathway alterations in HCC leveraging multi-platform profiling of patient tumor samples. Methods: 780 HCC tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) were analyzed. Clock gene Score (CS) was determined using expression of core clock genes Z scores (positives of CLOCK, ARNTL, RORA/B/C and negatives of repressors CRY1/2, PER1/2/3, REV Baba/B) stratified by quartiles. xCell was used to quantify cell infiltration in the tumor microenvironment (TME). Significance was determined as P-values and adjusted for multiple testing (q) of < .05. Gene expression profiles were analyzed for transcriptional signatures predictive of response to immunotherapy including the T cell inflamed score (TIS) and IFG score. Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for comparison. Results: CS was higher in metastatic sites than primary tumors (median transcripts per million [TPM]: 0.81 vs 0.37, P < .05). No significant differences in patient age and sex were observed between CS Q1 (lowest) and Q4 (highest) cohorts, although a trend towards a higher frequency of males was observed in Q4 (76% vs 52%, Q4 vs Q1, P = .04) and negatively correlated with FGF3 copy number amplification (2% vs 6%, P = .04) and WEE1 gene expression (median TPM: 15 vs 28, q < .05). No dMMR/MSI-H tumors were observed in our series and there were no significant associations with tumor mutational burden and PD-L1 protein expression. Expression of immune related genes was lower in tumors with high CS, including IDO1, CD80, PD-L1, LAG3, CD86, TIM3, PD-1 and PD-L2 (fold change: 0.57-0.67 q < .05). NK cell infiltration in the TME and the TIS score were also significantly lower in CS-high HCC (q < .05). Individually, lower CLOCK and CRY1 tumor mRNA expression were associated with longer OS (Q1 vs Q4: CLOCK HR 0.71, 95%CI [0.51-0.98], P = .04 and CRY1 HR 0.70 [0.51-0.95], P = .02, respectively). Conclusions: This is the most extensive profiling study to investigate the expression of clock genes in HCC. Our data show that clock genes expression impacts patient survival and is associated with alterations in immune-related gene expression and TIS score which suggest a role in the modulation of anti-tumor immunity. These results support the clock pathway role as a oncogenic driver and its potential as a therapeutic target in HCC. Research Sponsor: This work was partly supported by National Cancer Institute (P30CA14089), Gloria Borges WunderGlo Foundation, Dhton Family Foundation, Gene Gregg Pancreas Research Fund, San Pedro Peninsula Cancer Guild; Daniel Butler Research Fund, V foundation for cancer research, Victoria and Philip Wilson Research Fund, Fong research project and Ming Hsieh research fund.
Evaluating racial disparities for patients with advanced hepatocellular carcinoma (HCC) receiving first line immunotherapy within an equal access system.

Lauren Diaz Boyle, Munaf Alkadimi, Maria Elena Fierro, Kana Lucero, Kathleen Franklin, Michael Mader, Zohra Nooruddin; The University of Texas Health Science Center-San Antonio, San Antonio, TX; UTHSCSA, San Antonio, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; South Texas Veterans Health Care System, San Antonio, TX; University of Texas Health San Antonio, San Antonio, TX

Background: The incidence and mortality of HCC are increasing in the USA. HCC disparities have been reported across the entirety of the cancer timeline, from screening to local and systemic treatment and liver transplant. We aim to analyze the clinical characteristics, outcomes, and racial disparities in patients with advanced HCC receiving first-line Atezolizumab plus Bevacizumab (A+B) in the Veterans Health Administration (VHA) – the only health care system in the USA that provides equal access to all patients. Methods: Patients were followed from their A+B initiation date through the earliest of the last VHA visit, loss to follow-up, death, or end of study on Jan 31, 2023. Structured electronic health record and chart review data were retrospectively collected to determine patient baseline characteristics, including self-reported race, number of A+B doses, treatment response, subsequent line of treatment, length of follow-up, and overall survival (OS). The Chi-Squared test was used to compare rates, and Mann-Whitney test was used to compare medians. Results: Three hundred twenty-five patients were included. 64% were non-Hispanic White (NHW), and 36% were all other (AO) ethnicities or races combined (26% Black, 8% Hispanic, 2% Asian or Indigenous). The median age for each cohort was similar (66 years for AO vs. 68 for NHW), and ECOG performance was 1 in nearly 90% of each cohort. Viral hepatitis accounted for 70% and 48% of AO and NHW, respectively (p=0.0001). Despite clinical differences in OS and progression free survival (PFS), they were not statistically significant. Conclusions: Our VHA real-world data shows that despite having statistically significant etiologies, there was no statistically significant difference in the PFS and OS of patients with advanced HCC receiving first-line A+B in an equal access care system. This study supports our group’s findings in other malignant cohorts within VHA where equal healthcare access can mitigate other socio-demographic and biological factors. Research Sponsor: None.

<table>
<thead>
<tr>
<th>Survival and response rates by race/ethnicity.</th>
<th>NHW N=208</th>
<th>AO N=117</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time from diagnosis to initiation of A+B treatment, months</td>
<td>11.0 (2.3 – 33.5)</td>
<td>19.3 (3.1 – 34.3)</td>
<td>0.36</td>
</tr>
<tr>
<td>Number of Atezol/Bev doses, median</td>
<td>5 (3 – 11)</td>
<td>6 (3 – 15)</td>
<td>0.22</td>
</tr>
<tr>
<td>OS: 6 mo</td>
<td>149 (71.6%)</td>
<td>88 (75.2%)</td>
<td>0.49</td>
</tr>
<tr>
<td>OS: 1 yr</td>
<td>89 (47.3%)</td>
<td>64 (58.7%)</td>
<td>0.059</td>
</tr>
<tr>
<td>Objective Response Rate (CR + PR)</td>
<td>57 (27.4%)</td>
<td>37 (33.4%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Disease Control Rate (CR + PR +SD)</td>
<td>125 (60.1%)</td>
<td>66 (59.5%)</td>
<td>0.91</td>
</tr>
<tr>
<td>PFS: 6 mo</td>
<td>116 (57.7%)</td>
<td>66 (60.0%)</td>
<td>0.70</td>
</tr>
<tr>
<td>PFS: 1 yr</td>
<td>59 (28.8%)</td>
<td>42 (41.2%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Duration of Response (CR,PR,SD), months</td>
<td>8.7 (4.5 – 16.7)</td>
<td>11.7 (5.7 – 20.4)</td>
<td>0.029</td>
</tr>
<tr>
<td>Overall Survival Time, months</td>
<td>10.3 (5.0 – 20.4)</td>
<td>14.9 (6.0 – 20.4)</td>
<td>0.091</td>
</tr>
</tbody>
</table>
The clinical feasibility of circulating tumor DNA alterations in patients with advanced hepatocellular carcinoma.

Gwangil Kim, Sohyun Hwang, Haeyoun Kang, Jaekyung Cheon, Beodeul Kang, Chan Kim, Hong Jae Chon; Department of Pathology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea; CHA University School of Medicine, Seongnam, South Korea; Department of Pathology, CHA Bundang Medical Center, Seongnam, South Korea; Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea; Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea

Background: Need for individualized treatment based on tumor attributes is being reinforced with the rapid development of targeted therapies and immune checkpoint inhibitors for hepatocellular carcinoma (HCC). Lack of mandatory tissue biopsy for the diagnosis of HCC, continues to be a challenge for development of precision medicine for HCC compared to other solid tumors. Liquid biopsy enables comprehensive genomic profiling of circulating tumor DNA (ctDNA) shed from tumors into the circulation. This could compensate for the lack of tissue-based analysis in HCC providing a non-invasive and safer option for genomic profiling. This study aims to address the concordance between commercially available ctDNA and tissue genomic profiling in patients with advanced HCC and to assess the feasibility of liquid biopsy in the treatment of patients with HCC. Methods: Patients subjected to tissue-based next-generation sequencing (NGS) before systemic therapy for advanced HCC at CHA Bundang Medical Center from June 2020 to October 2022 and also had sufficient plasma samples available for ctDNA analysis were included. Oncomine Comprehensive Assay (OCA) Thermo-Fisher was used for tissue-based NGS and Guardant360 for ctDNA based NGS. For the concordance assessment for the same patient, paired samples of ctDNA and tumor tissue, we investigated the common targeted regions across both the panels. Results: Out of hundred thirty patients included in this study, 98% percent of ctDNA samples for these patients were successfully sequenced; ctDNA were detected in 88% of the samples. For the assessment of concordance between intra-patient ctDNA and tumor tissues, we investigated only clinically important (AMP/ASCO/CAP guidelines tier 1 or 2) variants. When we considered the variants detected in tissues as true positive, the concordance between the mutations detected from ctDNA and tissue samples indicated 68.9% sensitivity and 63.1% positive predictive value (PPV). In ctDNA, targetable alterations were detected in 16.9% of samples, such as ARID1A mutations (7.7%), PTEN mutations (6.9%), PIK3CA hotspot mutations (1.5%), RAS mutations (1.5%), and one RET fusion (0.8%). Regarding the concordance between ctDNA and tumor tissue, the sensitivity for mutation was high for RAS mutation (100.0%), PTEN mutations (100.0%), and ARID1A mutations (75.0%) but low for PIK3CA hotspot mutations (0.0%). One RET fusion was identified only in ctDNA. Conclusions: ctDNA-based genotyping demonstrated clinically acceptable concordance with tissue genomic profiling in patients with advanced HCC. Thus, liquid biopsy using ctDNA help address any challenges associated with the limited use of tissue-based genomic profiling in HCC. Investigation of time between blood and tissue collection and the impact it has on concordance is ongoing. Research Sponsor: This work was supported by the National Research Foundation of Korea [NRF] grant funded by the Korea government [MSIT] [NRF-2020R1C1C1010722 to HJC].
Lenvatinib (LEN) combined with tislelizumab (TIS) plus transcatheter arterial chemo-embolization (TACE) for unresectable hepatocellular carcinoma (uHCC): A single-arm, phase II clinical trial.

Xiang Nong, Yu-Mei Zhang, Jing-Chang Liang, Jin-Long Xie, Zhi-Ming Zhang; Guangxi Medical University Cancer Hospital, Nanning, China; Guangxi Medical University Cancer Hospital, Nanning, China

Background: uHCC still lacks effective treatments, combination of antiangiogenic targeted drugs and immune checkpoint inhibitors showed promising efficacy. TACE induces tumor necrosis and tumor antigen release, may synergize with immunotherapy. This study was to evaluate the efficacy and safety of TACE in combination with TIS and LEN in patients with uHCC. Methods: This study was a single-center, single-arm, open-label phase II exploratory clinical study (NCT05131698). Eligible patients were BCLC C stage and not candidates for surgical resection or liver transplantation, at least one target lesion evaluable, ECOG performance status of ≤1, and Child-pugh grade A or B. Enrolled patients received TACE treatment (loplatin + raltitrexed + iodine oil) followed by TIS (200 mg, IV, on Day 1 of a 21-day cycle) and LEN (body weight ≥ 60 kg: 12 mg/day; < 60 kg: 8 mg/day) daily. The primary endpoint was overall response rate (ORR) by mRECIST. The secondary endpoints included disease control rate (DCR), overall survival (OS), and progression-free survival (PFS) and safety. Results: As of December 28, 2022, 31 enrolled patients with uHCC were treated. Median follow-up time is 11.3 months. Among all patients with BCLC C, 28 patients (90.3%) had microvascular invasion and 17 (54.8%) had portal vein tumor thrombus. As assessed by mRECIST, the ORR and DCR were 71.1% and 87.1%, respectively (2 CR, 6.6%; 20 PR, 64.5%; 5 SD, 16.1%), 4 patients developed tumor progression (12.9%). As assessed by RECIST 1.1, the ORR and DCR were 67.7% and 87.1%, respectively (1 CR, 3.2%; 20 PR, 64.5%; 6 SD, 19.4%), 4 patients developed tumor progression (12.9%). The median PFS was 10.2 months (95% CI: 4.5-NA), and the median OS was not reached. Any grade treatment-emergent adverse events (TEAEs) occurred in 64.5% (20/31) patients. The most common TEAEs were Increased g-glutamyl transpeptidase (35%), Increased aspartate aminotransferase (32%), thrombopenia (25%). Only 2 patients experienced grade 3 TEAE (pneumonia). No serious adverse events (SAEs) were reported. Conclusions: In this study, TACE combined with TIS and LEN showed preliminary antitumor efficacy and tolerable safety profile in uHCC. Clinical trial information: NCT05131698. Research Sponsor: BeiGene biopharma incorporation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mRECIST</td>
</tr>
<tr>
<td>Confirmed objective response, n (% [95% CI])</td>
<td>22 (71.1% [52.0-85.8])</td>
</tr>
<tr>
<td>Complete response, n ( % )</td>
<td>2 (6.6%)</td>
</tr>
<tr>
<td>Partial response, n ( % )</td>
<td>20 (64.5%)</td>
</tr>
<tr>
<td>Stable disease, n ( % )</td>
<td>5 (16.1%)</td>
</tr>
<tr>
<td>Disease control, n (%[95% CI])</td>
<td>26 (87.1% [70.2-96.4])</td>
</tr>
<tr>
<td>Progressive disease, n ( % )</td>
<td>4 (12.9%)</td>
</tr>
</tbody>
</table>
Molecular subtypes from comprehensive clustering from multi-omics dataset to predict the therapeutic efficacy of immunotherapeutic agent-based treatments in advanced hepatocellular carcinoma.

Hong Jae Chon, Sung Hwan Lee, Gwangil Kim, Haeyoun Kang, Jaekyung Cheon, Beodeul Kang, Chan Kim; Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea; CHA Bundang Medical Center, Seongnam-Si, South Korea; Department of Pathology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea; Department of Pathology, CHA Bundang Medical Center, Seongnam, South Korea; Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea

**Background:** In advanced hepatocellular carcinoma (HCC), combined treatment using anti-PD-L1 and anti-VEGF antibodies is a major therapeutic strategy in addition to using anti-PD-1 and anti-CTLA4 target agents. To identify clinically relevant molecular biomarkers for immunotherapeutic agents-based treatment in advanced HCC by comprehensive molecular profiling using genomics alterations and transcriptomic data.

**Methods:** Multi-omics data from clinical tumor samples of patients treated with atezolizumab + bevacizumab (94 patients), nivolumab (40 patients), and ipilimumab + nivolumab (32 patients) were obtained from tumor biopsies or surgical resections in a single institution. The targeted panel sequencing was conducted via the Oncomine comprehensive assay (ThermoFisher, USA). QuantSeq mRNA sequencing (Lexogen, USA) was used to generate datasets for the genomic alterations and gene expression profiles.

**Results:** A total of 166 target sequences for genomic alterations and 136 transcriptomic sequences were performed in patients with advanced HCC treated with immunotherapeutic agent-based treatment options. High tumor mutation burden was significantly associated with favorable therapeutic efficacy (disease control rate, P=0.036) and progression-free survival (P=0.037) in patients who had atezolizumab with bevacizumab treatment. The genomic alteration of CTNNB1 mutation correlated with the favorable therapeutic efficacy of nivolumab monotherapy (PFS, P=0.022), contrary to TP53 mutation (PFS, P=0.063) which demonstrated unfavorable outcomes. CD274 (PD-L1) mRNA expression was significantly associated with a high drug response following nivolumab monotherapy (objective response rate, P=0.047) and oncologic outcomes (PFS, P=0.021). Interestingly, PLA2G4A, known as a downstream molecule of the VEGF signaling pathway, was highly correlated with unfavorable therapeutic efficacy of the combined atezolizumab with bevacizumab treatment (disease control rate, P=0.002) and related oncologic outcomes (PFS, P=0.003). We also identified the clinically relevant molecular subtypes from unbiased clustering using the ontologic pathway collection. We also used gene expression profiles to predict the therapeutic response and oncologic outcomes from immunotherapeutic agent-based treatment options.

**Conclusions:** We identified clinically relevant molecular biomarkers from comprehensive clustering of a multi-omics dataset to predict the therapeutic efficacy and oncologic outcomes. Further prospective studies with clinical validation are warranted to confirm clinical implications. Research Sponsor: This work was supported by the National Research Foundation of Korea [NRF] grant funded by the Korea government [MSIT] [NRF-2020R1C1C1010722 to HJC, NRF-2020R1A2C2004530 to CK].

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Phase 2 multicenter trial of rucaparib and nivolumab as maintenance therapy following first-line platinum-based chemotherapy in patients with advanced biliary tract cancer (BTC): BilT-02.

Vaibhav Sahai, Kent A. Griffith, Laura Williams Goff, Oxana V. Crysler, Thomas Enzler, Mark Zalupski; University of Michigan, Ann Arbor, MI; Center for Cancer Biostatistics, University of Michigan School of Public Health, Ann Arbor, MI; Vanderbilt University Medical Center, Nashville, TN

Background: Gemcitabine, cisplatin and durvalumab followed by maintenance durvalumab is standard of care first-line (1L) therapy for patients (pts) with advanced BTC. In this trial, we investigated the combination of a PARP inhibitor with anti-PD1 antibody in absence of progression after at least 4 months of standard 1L platinum-based chemotherapy. Methods: Pts with advanced BTC, ECOG PS 0-1 and absence of progression on 1L platinum-based therapy were enrolled on a phase 2 trial to receive rucaparib 600 mg PO BID in combination with nivolumab 240 mg IV Q2 weeks every 28 days for up to 2 years. The primary endpoint was 4-month progression-free survival (PFS) rate from the date of first study treatment with an alternative hypothesis of 85%. Secondary endpoints included median PFS and overall survival (OS) from first study treatment (PFS1, OS1) as well as from start date of first-line chemotherapy (PFS2, OS2), best overall response, and safety. Results: 31 pts were enrolled of which 14 (45%) were women, 25 (80.6%) Caucasian and 24 (77.64%) with ECOG 1. Primary disease site was intrahepatic, extrahepatic hilar and distal, and gallbladder cancer in 21 (67.7%), 4 (12.9%), 1 (3.2%) and 4 (12.9%), respectively. 1L platinum-based treatment included gemcitabine/cisplatin based in 26 (83.9%), FOLFOX in 3 (9.7%) and carboplatin/paclitaxel in 1 (3.2%) pts. Mean (range) cycles of rucaparib and nivolumab were 6.75 (1-24) and 5.9 (1-24). The median follow-up time is 28.7 months using reverse censoring methodology. PFS rate at 4 months was 54.8% (95% CI, 36-70.3), comparable to the 63% null estimate based on ABC-02 trial. Median PFS1 and OS1 are estimated to be 4.6 months (95% CI, 3.7-6.2) and 15.9 months (95% CI, 9.8-24.1). Median PFS2 and OS2 calculated from date of 1L chemotherapy are estimated as 9.9 months (95% CI, 8.3-11.3) and 21.4 months (95% CI, 14.8-26.7). Two (6.4%) pts had partial response (with IDH R132G and KRAS G12D) as best response with stable disease in an additional 22 (71%) pts. Mean (range) cycles of rucaparib and nivolumab were 6.75 (1-24) and 5.9 (1-24). The median follow-up time is 28.7 months using reverse censoring methodology. PFS rate at 4 months was 54.8% (95% CI, 36-70.3), comparable to the 63% null estimate based on ABC-02 trial. Median PFS1 and OS1 are estimated to be 4.6 months (95% CI, 3.7-6.2) and 15.9 months (95% CI, 9.8-24.1). Median PFS2 and OS2 calculated from date of 1L chemotherapy are estimated as 9.9 months (95% CI, 8.3-11.3) and 21.4 months (95% CI, 14.8-26.7). Two (6.4%) pts had partial response (with IDH R132G and KRAS G12D) as best response with stable disease in an additional 22 (71%) pts. Grade 3-5 treatment-related adverse events (TRAEs) occurred in 15 (48.4%) pts, including 1 patient who died on therapy due to possibly-related immune-related myocarditis. The most common grade 2 or greater TRAEs included fatigue (9, 29.0%), anemia (7, 22.6%), neutropenia (6, 19.3%), elevated AST (5, 16.1%) and elevated ALT (4, 12.9%). Reasons for treatment discontinuation included death (2), progression (27), adverse event (1) while 1 patient completed 2 years of study treatment. Conclusions: The primary endpoint of PFS rate at 4 months was not met but the preliminary measures of PFS1 and OS1 are much longer than expected, and hypothesis generating for rational combination of PARP inhibitor with maintenance immunotherapy in this rare cancer. Exploratory endpoint of association of genomic analysis with efficacy is ongoing and will be discussed. Clinical trial information: NCT03639935. Research Sponsor: Clovis Oncology, Bristol Myers Squibb Pharmaceuticals; University of Michigan Rogel Cancer Center.
Tracking the evolving ecosystem of recurrent hepatocellular carcinoma after liver transplantation.

Zijie Zhang, Gaoyang Wang, Youqiong Ye, Hao Feng, Qiang Xia; Renji Hospital, affiliated to Shanghai Jiao Tong University, School of Medicine, Shanghai, China; Shanghai Institute of Immunology, Department of Immunology and Microbiology, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Liver transplant (LT) contributes to the cure of hepatocellular carcinoma (HCC) by extending the conventional surgical margin, while removing the concurrent tumor-favoring conditions of the diseased liver. Over the past two decades, HCC has emerged as a preferable indication for LT, accounting for 22-45% of the cases globally. However, despite the stringent selection criteria, recurrence still occurs in a substantial proportion of patients, leaving 10-13 months of median survival after tumor relapse. To address this challenge, a thorough exploration of molecular mechanism behind HCC recurrence after LT is required. Here, for the first time, we performed a comprehensive analysis to depict the evolving and unique ecosystem of HCC in the context of LT and immunosuppressant (IS) administration.

Methods: We retrospectively reviewed our biobank and collected 91 paired (primary tumors (PT) from the explant after LT and relapsed tumors (RT) from hepatectomy) FFPE tumor samples from 15 patients for whole exome sequencing (WES). Also, from Jan 2021, we prospectively collected surgical tumor specimens and their adjacent non-tumor tissues from 15 primary and 6 post-LT intrahepatic recurrence patients for single-cell RNA sequencing. Moreover, 6 paired samples from 3 patients were used for spatial transcriptomic analysis.

Results: By analysing WES data, we confirmed that RT samples represent recurrent, instead of de novo tumors. Also, the phylogenetic analysis demonstrated strong clonal relationship between PT and RT based on shared SNVs. As to mutation landscape differences of PT and RT, we identified a significantly enriched mutation panel from RT, including MUC16, FAT3, APOB, COL6A3 and POTEC. And the accuracy of this panel for post-LT HCC recurrence surveillance using plasma derived cfDNA sequencing has been preliminarily validated in a prospective cohort of 17 patients. From the single-cell profiling, distinct immune microenvironment between PT and RT is identified. As predicted, proliferating T cells are decreased in RT due to IS. Pseudotime analysis of T cells revealed that T cells from PT mainly distribute at the terminal end of cytotoxic stage whereas T cells from RT mostly represent a naive state, further confirming the T cell blocking effect of IS. In terms of myeloid cells, we surprisingly found that FOLR2+ tumor associated macrophages, which is conventionally considered as a favorable prognosis factor, is increased in RT. Spatial transcriptomics and IHC also confirmed their active interplay with tumor cells at invasive margin. We postulate that such increase might be a result of the healthy nature of liver graft.

Conclusions: Our comprehensive dissection of the HCC ecosystem provides deeper insights into the tumor relapse after LT. Targeting novel mutations and strengthen the antigen presenting process between increased TAM and disabled T cells can be the future direction in this field. Clinical trial information: NCT04506398. Research Sponsor: None.
Geographical and baseline clinical characteristics of participants enrolled in hepatocellular carcinoma (HCC) trials: Analysis of US FDA approvals.

M. Naomi Horiba, Shruti U. Gandhy, Sandra J. Casak, Steven Lemery, Paul Kluetz, Richard Pazdur, Lola A. Fashoyin-Aje; FDA, Silver Spring, MD; FDA/CDER, Beltsville, MD; U.S. Food and Drug Administration, Silver Spring, MD; US Food and Drug Administration, Rockville, MD; Oncology Center of Excellence, U.S. Food and Drug Administration, Silver Spring, MD; Oncology Center of Excellence, U.S. Food and Drug Administration; Office of Oncologic Diseases, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD; US Food and Drug Administration, Silver Spring, MD

Background: Globalization of drug development is increasing, with reliance on data from patients accrued to large, randomized studies across continents. In addition to appropriate racial/ethnic representation, trials submitted to support FDA approvals should reflect the etiology and treatment patterns of HCC in the US. We conducted a pooled analysis of patient-level data from the HCC trials supporting approved marketing applications in the US to characterize geographical and baseline variables in clinical trials. Methods: Datasets from applications which received FDA approval for HCC between 2010-2022 were identified. The following data was abstracted: country, baseline disease characteristics (median age, HCC etiology, extent of tumor, and Child-Pugh score), and prior treatments received. Geographical region was recoded using categories observed by the United Nations M49 standard, based on country of enrollment reported in the datasets. Results: Variables that were defined differently across studies included region of enrollment, some categories of etiology, and prior therapy. Overall, the rate of HBV etiology was higher than that observed among patients with HCC in the US (20%), while the rate of HCV etiology was lower than in the US (50%). Conclusions: Variability in patient populations exist across trials submitted to FDA based on the regions that were targeted for enrollment and eligibility criteria. Global trials may be appropriate to support drug approvals for HCC; however, to ensure results are applicable to US patients, sponsors should select sites that represent a similar population with respect to racial/ethnic representation, disease etiology, and treatment patterns. Research Sponsor: None.

<table>
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<th>Geographic Region (%)</th>
<th>Trial 1* (n=602)</th>
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Baseline Characteristics (%)

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<th>MVI/EHS</th>
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<th>Prior Nonsystemic Therapy (%)</th>
<th>Locoregional</th>
<th>Resection</th>
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* Trial 1 SHARP (sorafenib); Trial 2 RESORCE (regorafenib); Trial 3 REFLECT (lenvatinib); Trial 4 CELESTIAL (cabozantinib); Trial 5 REACH-2 (ramucirumab); Trial 6 IMbrave150 (atezolizumab/bevacizumab); Trial 7 HIMALAYA (durvalumab/tremelimumab). † For sorafenib, data sources are FDA review and applicant’s study report. ‡ Americas are North, South, and Central America. Oceania is Australia, New Zealand, and Pacific Islands. ‡‡ Prior anticancer procedures. †† Transarterial chemoeembolization. 400 was an eligibility criterion. MVI/EHS = macrovascular invasion or extrahepatic spread; na = not available.
Effect of MYC-targeting programmable epigenetic mRNA therapeutics on TME and immunotherapy responses.

Yan Moore, William Senapedis, Kayleigh Gallagher, Elmer Figueroa, Madison Pacaro, Defne Yarar, Eugene Lee, Thomas McCauley; Omega Therapeutics, Cambridge, MA

Background: c-MYC is a master transcription factor (TF) critical for multiple cell physiologies. As a pleiotropic TF, MYC regulates the tumor microenvironment (TME) and impacts cancer cell initiation, growth, and survival. Although MYC expression is normally tightly controlled in normal cells, its activity is frequently dysregulated in cancer (e.g., HCC, NSCLC, Burkitt’s lymphoma). A direct MYC targeting anti-cancer agent has remained elusive, largely due the absence of a drug binding pocket and tight autoregulation. The MYC gene and its regulatory elements reside alone within an insulated genomic domain and represents a potential target for gene regulation via an epigenetic approach. Methods: We are developing programmable epigenetic mRNA medicines designed to controllably tune gene expression pre-transcriptionally with high specificity and durability. We have rationally designed MYC-targeted Omega Epigenomic (MYC-OEC: clinical candidate OTX-2002; MYC Lung OEC; mouse surrogate muMYC-OEC) to downregulate MYC expression, thereby selectively killing cancer cells while sparing normal cells. We investigated the role of MYC-OEcs in the modulation of the TME and demonstrated in human and mouse tumor models that MYC-OEcs enhanced the host immune response. Results: In HCC and NSCLC cell lines (Hep 3B, SKHEP1, H2009 and H460), treatment with MYC-OEcs in vitro significantly inhibited PD-L1 surface expression. Using the muMYC-OEC in vivo, we demonstrated tumor growth inhibition (TGI) in Hepa1-6 liver cancer syngeneic tumor models with 70% of the mice exhibiting complete tumor response with good tolerability. Cancer cells used to rechallenge the cured mice failed to grow, demonstrating that muMYC-OEC monotherapy induced immune memory. In addition to inhibiting tumor growth with either muMYC-OEC or checkpoint blockade immunotherapy (CBI; anti-PD-1 or anti-PD-L1) treatment, combination therapy further enhanced TGI. Tumor-infiltrating lymphocyte profiling demonstrated an increase in activated T cells and a reduction in Tregs following combination treatment, resulting in an increased effector T cell to Treg ratio over monotherapy. Depletion of CD4⁺, CD8⁺ and NK cells in vivo prior to single agent or combination treatment demonstrated a requirement for both CD4⁺ and CD8⁺ T cell activity for TGI. NK cells were dispensable. Taken together, these data demonstrate that the improved CBI/MYC-OEC combination activity is mediated through the recruitment of activated T cells and reduction of immune suppressive Tregs. Conclusions: These efficacy and tolerability data support the combination of MYC-OEC and CBI treatment in patients with solid tumors. OTX-2002 is currently being evaluated in a Phase 1/2 clinical trial as a monotherapy and in combination with SoC (i.e., TKI and CBIs) for patients with HCC and other solid tumor types known for an association with MYC. Research Sponsor: Omega Therapeutics.
FDA analysis of treatment efficacy based on etiology of hepatocellular carcinoma.

May Tun Saung, Jiaxin Fan, Joyce Cheng, Yuan-Li Shen, Sandra J. Casak, Steven Lemery, Lola A. Fashoyin-Aje; US Food and Drug Administration, Silver Spring, MD; FDA, Silver Spring, MD; Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD; United States Food and Drug Administration, Silver Spring, MD; U.S. Food and Drug Administration, Silver Spring, MD

**Background:** Retrospective analyses of trial-level data report that etiology of hepatocellular carcinoma (HCC) (e.g., viral versus [vs.] non-viral) may influence efficacy of systemic therapies used in advanced HCC. FDA conducted an analysis of 9 randomized controlled trials (RCTs; n=5,417) to assess treatment effects based on drug class, treatment line, and HCC etiology.

**Methods:** FDA conducted a retrospective, exploratory analysis of 3 RCTs comparing first line (1L) treatment with anti-programmed cell death (ligand)-1-containing regimens (αPD-(L)1) to single-agent anti-vascular endothelial growth factor therapy (αVEGF), and 6 RCTs comparing second line (2L) treatment consisting of αPD-(L)1 or αVEGF to placebo. For each line of treatment (1L or 2L), meta-analyses of overall survival (OS) were performed for the overall treatment effect and by disease etiology, viral (hepatitis B [HBV], or hepatitis C [HCV]) vs. non-viral. Subgroup analyses were performed to investigate the confounding effect of subsequent therapy (yes vs. no) and region (Asian vs. non-Asian) on etiology. Trial-level hazard ratios (HRs) and 95% confidence intervals (CI) were mostly calculated using patient-level data submitted to FDA. Pooled HRs and CIs were calculated using a random-effects model.

**Results:** While 1L αPD-(L)1 improved OS compared to 1L αVEGF in the overall population (HR [95% CI]: 0.8 [0.73, 0.88]), treatment effects were comparable for viral (HR [95% CI]: 0.75 [0.6, 0.92]; n=1,435) and non-viral (HR [95% CI]: 0.83 [0.72, 0.95]; n=979) subgroup analyses, and not influenced by subsequent therapy or region. Analyses based on specific viral infection (i.e., HBV or HCV), showed that improvement in OS for αPD-(L)1 vs. αVEGF appeared larger for HBV (HR [95% CI]: 0.7 [0.59, 0.82]; n=833) compared to HCV (HR [95% CI]: 0.83 [0.6, 1.16]; n=602). Treatment effects were also comparable in 2L for different etiologies for both αPD-(L)1 (HR [95% CI] for viral: 0.76 [0.62, 0.93]; n=529 and non-viral: 0.85 [0.65, 1.11]; n=337) and αVEGF (HR [95% CI] for viral: 0.79 [0.69, 0.9]; n=1,288 and non-viral: 0.74 [0.63, 0.88]; n=849), and not influenced by subsequent therapy. Nonetheless, compared to placebo, αPD-(L)1 had a larger treatment effect with HBV (HR [95% CI]: 0.69 [0.5, 0.94]; n=459) compared to non-viral etiologies.

**Conclusions:** The results did not demonstrate that etiology of HCC was predictive of OS for both treatment classes based on retrospective, exploratory meta-analyses of 9 RCTs; however, the treatment effects may be more pronounced in patients with HBV who received αPD-(L)1 as 1L or 2L. Uncertainty remains regarding subgroup treatment effects given limited number of trials in the analyses (mostly leading to approvals), overlapping CIs, number of patients in some subgroups, retrospective nature, and exclusion of trials with inadequate data regarding etiology of HCC. Research Sponsor: None.
Characteristics and outcomes of patients with young-onset versus average-onset cholangiocarcinoma in the United States.

Udhayvir Singh Grewal, Rikeenkumar Dhaduk, Sagar Patel, Achintya D Singh, Justin James Chau, Sakti Chakrabarti; University of Iowa Hospitals and Clinics, Iowa City, IA; St Jude Children’s Research Hospital, Memphis, TN; Landmark Medical Center, Woonsocket, RI; Metro Health Medical Center, Cleveland, OH; University Hospital Seidman Cancer Center, Cleveland, OH

Background: Cholangiocarcinoma (CCA) is a lethal malignancy originating from the epithelium lining the biliary tree, with a rising incidence in the Western world. CCA is commonly diagnosed after the age of 50 years, referred to as average-onset CCA (AOCCA), which has known risk factors and predictors of overall outcomes. However, robust data regarding the characteristics and outcomes of patients with young-onset (diagnosed <50 years of age) CCA (YOCCA) are lacking.

Methods: Data on patient characteristics, tumor characteristics, incidence, and mortality were retrieved from the SEER database spanning a period from the year 2000 to 2017 (representing 48% of the US population). Intrahepatic CCA (iCCA) was identified with a topography code of C22.0 (liver) and a histology code of 8140, 8160, 8161, 8480, 8481, or 8500 or with a topography code of C22.1 (intrahepatic bile ducts) and a histology code of 8000, 8010, 8020, 8140, 8160, 8161, 8260, 8480, 8481, 8490, or 8500. Extrahepatic CCA (eCCA) was identified with a topography code of C24.1 (extrahepatic biliary ducts) and a histology code of 8000, 8010, 8020, 8140, 8160, 8161, 8260, 8480, 8481, 8490, or 8500, or for any case with a topography code of C22.0, C22.1, or C24.0 and a histology code of 8162 (Klatskin tumor). A comparison was made between the patients with YOCCA and AOCCA. Trends in incidence were analyzed using the Joinpoint regression model. Overall survival distributions were estimated using the Kaplan-Meier method.

Results: A total of 28,367 patients were included in the analysis, which included 2,082 (7.34%) patients with YOCCA. We noted an increase in the incidence of YOCCA over the study period (annual percentage change=+2.53, p=0.003). The majority of the patients in the YOCCA group were males (54.66%), White (50%), and had iCCA (71.9%). When compared to AOCCA, these patients were more likely to be males (54.7% vs 52.4%, p=0.048), non-White (39.8% vs 35.5%, p=0.007), and have a diagnosis of iCCA (71.9% vs 65.7%, p<0.0001). Patients in the YOCCA group were more likely to present with regional spread (31.6% vs 28.4%, p<0.0001) and metastatic disease (31.9% vs 25.6%, p<0.0001). YOCCA patients were also more likely to receive surgery (33.3% vs 22.7%, p<0.0001) and chemotherapy (62.6% vs 37.3%, p<0.0001) compared to patients in the AOCCA group. Patients with YOCCA had a significantly better median overall survival (13 months vs. 7 months, p<0.001) than patients with AOCCA.

Conclusions: The current analysis showed a significant increase in the incidence of YOCCA over the 17 years of the study period. Patients with YOCCA were more likely to be non-White, males and present with iCCA. Despite presentation with advanced-stage disease (with regional spread or metastatic disease), patients with YOCCA were more likely to receive cancer-directed therapy and had better overall survival than patients with AOCCA. Research Sponsor: None.
Adjuvant immune checkpoint inhibitors and association with recurrence-free survival in postoperative hepatocellular carcinoma (PREVENT): A prospective cohort study.

Le Li, Xiu-Mei Liang, Kang Chen, Guan-Lan Zhang, Shan Huang, Liang Ma, Jian-Hong Zhong; Guangxi Medical University Cancer Hospital, Nanning, China

Background: Adjuvant therapy may improve survival of patients with hepatocellular carcinoma (HCC) after curative resection, yet no such therapy is universally recommended. This study compared safety and efficacy outcomes between patients at high risk of recurrence who received different types of adjuvant therapy or no such therapy after hepatic resection for HCC. Methods: Recurrence-free survival (RFS), overall survival, and adverse events were compared among patients who received adjuvant immune checkpoint inhibitors (ICIs) alone, ICIs with tyrosine kinase inhibitors (TKIs), or no adjuvant therapy at our medical center between 13 March 2019 and 19 March 2022. In some analyses, patients who received adjuvant therapy were matched based on propensity scores to patients who did not, in order to reduce confounding due to baseline differences. This study was registered on ClinicalTrials.gov (NCT05221398).

Results: Of the 492 patients in our final analysis, 410 (83.3%) received no adjuvant therapy, 50 (10.2%) received ICIs alone, and 32 (6.5%) received adjuvant ICIs and TKIs. During median follow-up of 23.3 months (IQR 15.6 to 31.1 months), HCC recurred in 221 (53.9%) of patients who received no adjuvant therapy, compared to 22 (44.0%) of patients who received ICIs and 18 (56.3%) of patients who received ICIs and TKIs. RFS was significantly longer among patients who received either type of adjuvant therapy (23.9 months, 95%CI 14.0-33.7) than among those who received none (16.8 months, 95%CI 13.2-20.3), and this difference remained significant after propensity score matching (HR 0.61, 95%CI 0.39-0.94, P = 0.033). However, overall survival was unaffected by either type of adjuvant therapy, even after propensity score matching. The rate of grade 3 or 4 adverse events was similar between the two types of adjuvant therapy. Conclusions: ICIs alone or with TKIs may improve RFS of patients at high risk of recurrence after curative resection. Clinical trial information: NCT05221398. Research Sponsor: None.
Camrelizumab in combination with apatinib as a perioperative treatment for patients with hepatocellular carcinoma at high risk of recurrence: A prospective, single-arm, phase 2 study.

Yunlong Cui, Xu Bao, Ge Yu, Huikai Li, Feng Fang, Qiang Li, Wei Zhang, Qiang Wu, Lu Chen, Chen Liu, Tianqiang Song; Tianjin Medical University Cancer Hospital & Institute, Tianjin, China; Department of Hepatobiliary Surgery, Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention and Therapy, National Clinica, Tianjin, China; Liver Cancer Research Center for Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China; Liver Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Liver Cancer Research Center for Prevention and Therapy, National Clinica, Tianjin, China; Department of Hepatobiliary Surgery, Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention and Therapy, Tianjin’s Clinical Research Center for Cancer, Tianjin, China; Liver Cancer Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Department of Hepatobiliary Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, and a rising cause of cancer-related mortality. To date, the optimal perioperative treatment strategy for HCC patients remains unclear. It is urgent to develop novel and reliable therapeutic interventions to reduce the risk of recurrence and improve survival in patients with locally advanced HCC. Methods: This prospective, exploratory, single-arm, phase 2 study enrolled patients with primary resectable HCC who had not received prior systemic therapy. Before surgery, patients received combination treatment with four cycles of camrelizumab (200 mg, Q2W) plus apatinib (250 mg, QD). Each cycle was two weeks. The feasibility of hepatic resection was assessed by radiographic imaging. After 4–8 weeks of surgery, patients continued combination therapy (camrelizumab [200 mg, Q2W] and apatinib [250 mg, QD]) for one year. Primary endpoint was major pathological response (MPR). Secondary endpoints were pathologic complete response rate (pCR), objective response rate (ORR), disease-free survival (DFS), and safety. Exploratory endpoint was microvascular invasion (MVI). This study is registered on ClinicalTrials.gov, number NCT04701060. Results: Between Jan 12, 2021, and Aug 17, 2022, 31 patients with a median age of 54 years were enrolled. Among these, 21 patients (67.7%) had hepatitis B virus infection. Before surgical incision, two patients withdrew informed consent. Therefore, ORR based on RECIST 1.1 and mRECIST were 13.8% (4/29) and 48.3% (14/29), respectively. 26 patients underwent hepatic resection, R0 resection rate was 100%, 10 (38.5%) patients achieved MPR, and pCR rate was 7.7%. The reasons for patients not undergoing surgery were disease progression and serious adverse events (AEs). Among patients with MVI, M0 was found in 57.7% (15/26) patients, MI was found in 34.6% (9/26) patients, and M2 was found in 7.7% (2/26) patients. 1-year DFS rate was 77.4%, and median DFS was not reached. The most common AEs included increased aspartate aminotransferase (74.2%), increased alanine aminotransferase (70.1%), decreased platelet count (61.3%), anemia (58.1%), and decreased lymphocyte count (51.6%). Grade 4 AEs occurred in 7 of 31 patients, and there were no treatment-related deaths. Conclusions: Camrelizumab plus apatinib as a perioperative treatment is effective and tolerable in patients with HCC at high risk of recurrence. Preoperative neoadjuvant therapy has reduced the rate of MVI. Because of the short follow-up period, whether perioperative treatment can effectively reduce recurrence rates and improve long-term survival still needs further investigation. Clinical trial information: NCT04701060. Research Sponsor: Jiangsu Hengrui Medicine.
Machine learning-based multimodal prediction of prognosis in patients with resected intrahepatic cholangiocarcinoma.

Benoit Schmauch, Eliott Brion, Valérie Ducret, Naaz Nasar, Sarah McIntyre, Patrick Sin-Chan, Charles Maussion, William R. Jarnagin, Jayasree Chakraborty; OWKIN, Paris, France; Memorial Sloan Kettering Cancer Center, New York, NY; Regeneron Pharmaceuticals, Inc., New York City, NY

Background: Intrahepatic cholangiocarcinoma (iCCA) is an aggressive malignancy and the second most common primary liver cancer. About a third of patients may benefit from surgery but recurrence is common and the overall survival is low. Accurate prognosis modeling that can predict response to treatment and outcome remains an unmet clinical need. Deep learning methods provide a new opportunity to better predict prognosis by extracting distinguishing characteristics interrogating multiple data sources, which appears to be superior to unimodal modeling. This study aimed to construct a predictive model of patient outcome and identify predictive biomarkers based on a combination of clinical, genomic, histological and radiological data.

Methods: We analyzed 83 patients with iCCA that underwent surgery and designed a multi-modal model to predict overall survival (OS) and progression-free survival (PFS). Among these patients, each had one to three hematoxylin/eosin histology slides. As a pre-processing step, each histology slide was decomposed into patches, each patch was fed into a ResNet feature extractor to extract a feature representation of the patch, and the features across patches were aggregated with maximum pooling to yield a 2048-dimensional vector representation for each slide. Among these 83 patients, 76 patients had their tumors profiled for somatic genomic alterations using MSK-IMPACT, a deep targeted-sequencing assay. A binary matrix across altered genes and samples was created as an input to the prediction model. Cox proportional hazard models specific to each modality (clinical data, histological slides, and altered genes) were then designed and their predictions were averaged to produce the final log-risk score. The models were validated using a 5-fold, 5-repeat cross-validation with patient-level splits.

Results: A model using only clinical and routine histological data achieved a concordance index of 0.74 (95% confidence interval, 0.64-0.82) for OS and 0.73 (0.64-0.78) for PFS. Adding information about genetic alterations improved performance for OS (0.80, 0.70-0.88) and similar performance for PFS (0.72, 0.64-0.79). Both models outperform a staging-based patient stratification.

Conclusions: This study demonstrates that machine learning models can improve survival prediction using multi-modal data after resection of intrahepatic cholangiocarcinoma. Such models have the potential to improve risk stratification and treatment recommendations. Research Sponsor: OWKIN.

<table>
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<tr>
<th>Input data</th>
<th>OS</th>
<th>PFS</th>
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<tr>
<td>Cancer stage (AJCC/UICC 8th edition)</td>
<td>0.66 (0.55-0.75)</td>
<td>0.59 (0.49-0.66)</td>
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<tr>
<td>Clinical + Histological</td>
<td>0.74 (0.64-0.82)</td>
<td>0.73 (0.64-0.78)</td>
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<td>Clinical + Histological + Altered genes</td>
<td>0.80 (0.70-0.88)</td>
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Efficacy and safety of HepaSphere drug-eluting bead transarterial chemoembolization combined with hepatic arterial infusion chemotherapy in advanced hepatocellular carcinoma.

Baojiang Liu, Song Gao, Jianhai Guo, Fuxin Kou, Shaoxing Liu, Xin Zhang, Aiwei Feng, Xiaodong Wang, Guang Cao, Hui Chen, Peng Liu, Haifeng Xu, Qinzong Gao, Renjie Yang, Xu Zhu; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Interventional Therapy, Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Interventional Therapy, Peking University Cancer Hospital & Institute, Beijing, China

Background: Transarterial chemoembolization (TACE) is widely applied and shows good efficacy in advanced hepatocellular carcinoma (HCC). Recently, hepatic arterial infusion chemotherapy (HAIC) has also gained popularity in the treatment of HCC. Several studies have described the comparison between HAIC and TACE or TACE combined with HAIC. However, the evaluation between TACE plus HAIC and HAIC is rarely reported. Here, we observed the performance of HepaSphere DEB-TACE combined with HAIC (Hepa-HAIC) comparing to HAIC in patients with advanced HCC.

Methods: 167 patients diagnosed as advanced HCC and treated in Peking University Cancer Hospital from May 2018 to May 2022 were enrolled in this retrospective study, composed of 74 patients received HepaSphere DEB-TACE combined with HAIC (Hepa-HAIC) and 93 patients received HAIC-FOLFOX. More than 60% patients experienced other treatments before the enrollment. To avoid the selection bias, propensity score matching (PSM) was conducted and applied for the efficacy and safety analysis between these two cohorts. The primary endpoints are progression-free survival (PFS) and overall survival (OS); the secondary endpoint includes objective response rate (ORR), disease control rate (DCR) and safety.

Results: Propensity-matching yielded 48 pairs and the baselines were almost equal in Hepa-HAIC and HAIC cohorts after matching. Median PFS and median OS were both higher in matched Hepa-HAIC cohort (median PFS:8.9 vs. 5.8 months, P=0.035; median OS:22.4 vs. 9.5 months, P=0.027), which were consistent with pre-matching analysis. The ORR in Hepa-HAIC and HAIC cohorts was 75.0% and 37.5%, respectively; DCR was 93.8% after Hepa-HAIC and 81.3% after HAIC. There was no treatment-related death. Serious adverse events were similar in these two groups, except alanine aminotransferase (ALT) and vomiting. There was more frequency of Grade 3–4 ALT elevation in Hepa-HAIC (33.3% vs. 8.3%, P=0.003) while more incidence of vomiting in HAIC group (29.2% vs. 12.5%, P=0.044). Conclusions: All of the observed PFS, OS, ORR and DCR in Hepa-HAIC group are superior to HAIC group, which indicates the combination of HepaSphere DEB-TACE and HAIC may lead to improved outcomes with comparable safety profile in advanced HCC. Research Sponsor: None.

<table>
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<tr>
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<th>Hepa-HAIC (N=48)</th>
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<tr>
<td>DCR</td>
<td>93.8%</td>
<td>81.3%</td>
<td>&lt;0.001</td>
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<tr>
<td>mOS</td>
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Utility of circulating tumor DNA (ctDNA) as a predictive biomarker for disease monitoring in patients (pts) with cholangiocarcinoma (CCA) before and during adjuvant chemotherapy (ACT): Sub-analysis of the randomized phase 2 STAMP trial.

Changhoon Yoo, George Laliotis, Hyeyeun Jeong, Jae Ho Jeong, Kyu-Pyo Kim, Seonmin Lee, Baek-Yeol Ryoo, Shruti Sharma, Punashi Dutta, Meenakshi Malhotra, Adham J. Jurdi, Minetta Liu; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Natera, Inc, Austin, TX; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South); Digestive Disease Research Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Natera, Inc., Austin, TX; Natera, San Carlos, CA

Background: Detection of circulating tumor DNA (ctDNA) in blood is a powerful predictive biomarker for identifying molecular residual disease (MRD) post-surgery. Not much is known about the utility of identifying MRD using ctDNA in pts with resected CCA, despite its associated poor prognosis. The STAMP trial (NCT03079427), a randomized phase 2 study comparing adjuvant capecitabine (CAP) to gemcitabine plus cisplatin (GemCis) showed no difference in recurrence-free survival (RFS) and overall survival (OS) between the 2 arms. The goal of this analysis was to evaluate the feasibility of monitoring ctDNA to predict the risk of recurrence in pts with resected CCA.

Methods: A total of 254 plasma samples were collected from a cohort of 89 CCA (hilar, N = 43; distal, N = 46) pts post-surgery at 3 separate time points; pre-ACT (baseline, N = 89), on-ACT C5D1 (after 5 cycles of treatment) (N = 88), and on-ACT C8D1 (after 8 cycles of treatment) (N = 77). Longitudinal ctDNA testing was performed using a personalized, tumor-informed ctDNA assay (Signatera, bespoke mPCR-NGS assay). ctDNA results were analyzed and evaluated for its correlation with RFS and OS.

Results: At the MRD timepoint (baseline, pre-ACT), 24.7% (22/89) pts were ctDNA-positive, 90.9% (20/22) of whom recurred demonstrating a trend for shorter RFS (HR = 1.7, 95%CI 0.98-2.8, p = 0.069) compared to ctDNA-negative pts. All pts who remained ctDNA-positive on-ACT at C5D1 (N = 17) and C8D1 (N = 15), recurred clinically with a significantly shorter RFS (HR = 8.1, 95%CI 4.3-15, p < 0.0001 and HR = 5.0, 95%CI 2.7-9.4, p < 0.0001, respectively). The primary cancer site (hilar vs distal) or type of ACT (CAP vs GemCis) had no impact on RFS irrespective of ct-DNA result. Pts who remained ctDNA-negative on ACT (N = 56) showed significantly better RFS compared to pts who remained positive (N = 10, HR = 6.6, 95%CI 3.1-14, p < 0.001), or who turned positive (N = 11, HR = 5.2, 95%CI 2.5-10.5, p < 0.001). In multivariate analysis including primary tumor site, sex, pathological grade and ACT regimen, positive ctDNA status at baseline (pre-ACT) remained significant for poor RFS (HR = 1.82, 95%CI 1.04-3.18, p = 0.035).

Conclusions: Personalized monitoring of ctDNA both pre and on-ACT is feasible and predictive for recurrence in pts with resected CCA. To our best knowledge, this is one of the first reports presenting the clinical implication of ctDNA monitoring on ACT, in pts with CCA. Our findings suggest ctDNA monitoring may help optimize clinical decision-making in pts with resected CCA. Larger prospective studies would be needed to validate the findings of this study. Clinical trial information: NCT03079427. Research Sponsor: Natera; Asan Institution for Life Science.
Preliminary results of sequential transarterial chemoembolization and stereotactic body radiotherapy followed by immunotherapy using single tremelimumab regular interval durvalumab in locally advanced, unresectable hepatocellular carcinoma (START-FIT using STRIDE): A single-arm, phase II study.

Chi Leung Chiang, Stephen Lam Chang, Sik-Kwan Chan, Ann Shing Lee, Keith Wan Hang Chiu, Vanessa Ting Yan Yeung, Natalie Sean Man Wong, Venus Wan Yan Lee, Vince Wing Hang Lau, Nancy Kwan Man, Feng-Ming Spring Kong, Albert Chi Yan Chan; The University of Hong Kong, Hong Kong, NA, Hong Kong; The Chinese University of Hong Kong, Shatin, Hong Kong; Department of Clinical Oncology, The University of Hong Kong, Hong Kong, Hong Kong; Tuen Mun Hospital, Hong Kong, Hong Kong; University of Hong Kong, Hong Kong, Hong Kong; Prince of Wales Hospital, Hong Kong, Hong Kong; The University of Hong Kong, Hong Kong, Hong Kong; Clinical Oncology Medical Center of The University of Hong Kong-Shenzhen Hospital, Shenzhen, Guangdong, China; Department of Surgery, Queen Mary Hospital, Hong Kong, Hong Kong

Background: Sequential transarterial chemoembolization and stereotactic body radiotherapy followed by immunotherapy (IO) (START-FIT) using anti-PD-L1 has demonstrated promising efficacy in locally advanced HCC (laHCC). We aimed to evaluate START-FIT activity using anti-PD-L1 and anti-CTLA-4 IO backbone.

Methods: Adult patients with laHCC not suitable for curative resections were recruited. Each with tumor at least 5cm, maximum three tumors, and child-Pugh A5-B7 liver function. Patients had single TACE, 5-SBRT 28 days after, then single Tremelimumab (300mg) and regular 4-week interval Durvalumab (1500mg) at 7 days upon SBRT completion. Primary endpoint was overall response rate (ORR) per modified Response Evaluation Criteria in Solid Tumors (mRECIST); secondary endpoints included progression-free survival (PFS), overall survival (OS), and treatment-related (TR) adverse event (AE) [NCT04988945]. Results: During 11 Dec, 20 and 3 Oct, 22, 16 patients were enrolled with median age 66 (range: 51–84 years), 14 (87.5%) were male, the lesion(s) diameter median sum was 11.2 cm (r: 5.8–15cm), and 11 (68.8%) had macrovascular invasion (n=6, hepatic vein, n=4, branched portal vein, n=1 both). With median 11.3 months (r: 3.7–24.5 months) follow-up time, the best ORR was 81.3% (95% CI: 54.4–96.0%) (Complete response CR: n=7, 43.8%; partial response PR: n=6, 37.5%; static disease SD + progressive disease PD: n=3, 18.7%). The 6 and 12-month PFS rates was 86.7% (95% CI: 69.3–100%) and 58.7% (95% CI: 33.6–84.4%), while 6 and 12-month OS rates was 100% (95% CI: 91.7–100%) and 83.3% (95% CI: 62.2–100%) respectively. The 12-month OS with CR vs. PR vs. SD+PD was 100%, 75%, and 50% respectively. Four (25%) and one patient (6.3%) experienced TRAEs and immune-related AE of grade 3 or worse respectively.

Conclusions: START-FIT using STRIDE is safe and effective in unresectable laHCC resulted in 43.8% CR rate and promising survival. Clinical trial information: NCT04988945. Research Sponsor: Astra.
Primary analysis of a phase II study of atezolizumab plus bevacizumab for TACE-unsuitable patients with tumor burden beyond up-to-seven criteria in intermediate-stage hepatocellular carcinoma: REPLACEMENT study.

Kazuomi Ueshima, Masatoshi Kudo, Kaoru Tsuchiya, Naoya Kato, Tatsuya Yamashita, Shigeo Shimose, Kazushi Numata, Yuzo Kodama, Yasuhiito Tanaka, Hidekatsu Kuroda, Shinji Itoh, Hiroshi Aikata, Atsushi Hiraoka, Michihisa Moriguchi, Yoshiyuki Wada, Kauhiko Nakao, Ryosuke Tateishi, Sadahisa Ogasawara, Kouji Yamamoto, Masafumi Ikeda; Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan; Kindai University Faculty of Medicine, Osaka, Japan; Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashino, Japan; Chiba University, Graduate School of Medicine, Department of Gastroenterology, Chiba-Shi Chuo-Ku, Japan; Kanazawa University Hospital, Kanazawa, Japan; Kurume University Hospital, Kurume, Japan; Yokohama City University Medical Center, Yokohama, Japan; Department of Internal Medicine, Division of Gastroenterology, Kobe University Graduate School of Medicine, Kobe, Japan; Department of Gastroenterology and Hepatology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan; Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Iwate Medical University, Yahaba, Japan; Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Gastroenterology, Hiroshima Prefectural Hospital, Hiroshima, Japan; Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Japan; Kyoto Prefectural University of Medicine, Kyoto, Japan; National Hospital Organization Kyushu Medical Center, Fukuoka, Japan; Department of Gastroenterology and Hepatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; The University of Tokyo Hospital, Bunkyo-Ku, Japan; Graduate School of Medicine, Chiba University, Chiba, Japan; Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Intermediate-stage hepatocellular carcinoma (HCC) is a heterogeneous disease; therefore, the efficacy of transarterial chemoembolization (TACE) is affected by tumor burden, resulting in a wide range of survival outcomes. Multiple recent guidelines suggest that systemic therapy is preferable for patients with intermediate-stage HCC who are TACE unsuitable because of high tumor burden, such as beyond up-to-seven criteria. The Phase III IMbrave150 study established atezolizumab plus bevacizumab (atezo+bev) as the standard of care in patients with unresectable HCC. Here, we investigated whether atezo+bev is potentially superior to TACE in efficacy and safety in TACE-naive patients with unresectable intermediate-stage HCC beyond up-to-seven criteria. Methods: In this multicenter, phase II study, atezo 1200 mg + bev 15 mg/kg q3w were administered to eligible patients (as defined above plus having Child-Pugh A liver function) enrolled from Dec 2020 to Sep 2021 until discontinuation due to disease progression, adverse events (AEs), or other reasons. Overall survival (OS) follow-up continued for 2.5 years after enrolment. The primary endpoint was progression-free survival (PFS) assessed by mRECIST by investigator; secondary endpoints were objective response rate (ORR), PFS by RECIST v1.1, OS, and safety. In an exploratory analysis, we conducted propensity score matching (PSM) analysis to compare the efficacy between atezo+bev and TACE, the data of which were retrospectively collected in patients treated with TACE in each participating center from Jan 2017 to Dec 2017. Results: In total, 74 patients were enrolled (male, 87.8%; mean age, 73.7 years; median [range] maximum tumor diameter by pre-treatment CT, 4.8 [1.0,13.0] cm). Median (min, max) follow-up was 15.0 (1.6, 21.6) months. Median PFS was 9.1 (95%CI: 7.1, 10.2) months (by mRECIST; primary endpoint). ORR was 45.9 (95%CI: 34.3, 57.9)% by mRECIST. Median OS was not reached (NR) (95%CI: NR, NR). 12-month OS rate was 84.6 (95%CI: 74.0, 91.2)%%. The most frequent AEs (any grade ≥10% of patients) were hypertension, proteinuria, malaise, anorexia, edema, pruritis, and diarrhea. Conclusions: Atezo+bev provides clinical benefits to TACE-unsuitable patients with intermediate-stage HCC beyond up-to-seven criteria. Results of the exploratory PSM analysis will be presented. Clinical trial information: jrcts071200051. Research Sponsor: Chugai Pharmaceutical Co., Ltd.
A phase II/III study of camrelizumab plus apatinib as perioperative treatment of resectable hepatocellular carcinoma at intermediate-high risk of recurrence: Primary results of major pathologic response from phase II stage.

Jian Zhou, Jia Fan, Fang-Ming Gu, Tao Li, Dou-Sheng Bai, Hui-Chuan Sun, Zheng Wang, Shuang-Jian Qiu, Qing-Hai Ye, Ying-Hong Shi, Qiang Gao, Xiao-Ying Wang, Xin-Rong Yang, Guo-Ming Shi, Yuan-Fei Peng; Liver Cancer Institute, Zhongshan Hospital, and Key Laboratory of Carcinogenesis and Cancer Invasion (Ministry of Education), Fudan University, Shanghai, China; Third Affiliated Hospital of Naval Medical University (Eastern Hepatobiliary Surgery Hospital), Shanghai, China; Qilu Hospital of Shandong University, Jinan, China; Subei People’s Hospital, Yangzhou University, Yangzhou, China

Background: Surgical resection remains an important treatment strategy for patients (pts) with liver cancer. However, the 5-year recurrence rate is still 50-70% in surgically resectable pts. Intermediate-high risk factors of recurrence in HCC include single tumor size > 5 cm, multiple tumors, and microvascular invasion. The standardized perioperative regimen for resectable HCC has not been established. This study aimed to assess the efficacy and safety of camrelizumab plus apatinib (C+A) as a perioperative regimen in resectable HCC at intermediate-high risk of recurrence (Clinical trial: NCT04521153). Methods: In this multicentre, randomised, phase II/III study, eligible HCC pts (CNLC Ib-IIIA) were randomly assigned in a 1:1 ratio to treatment group and control group. Pts in treatment group received 2 cycles of C (200mg Q2W) plus A (250mg QD) followed by surgery and a post-surgical TACE. At least 6 cycles of sequential treatment of C (200mg Q3W) plus A (250mg QD) were performed after TACE. Pts in control group received surgical resection and a post-surgical TACE. Primary endpoint of phase III stage was 3-year EFS, of phase II stage was MPR (defined as less than 50% residual tumor) rate. In the phase II stage, futility analysis on a phase II outcome was performed after pts in treatment group completed surgical resection and pathological evaluation. If <15% of pts achieved an MPR, or >20% of pts had progression that precluded surgery, the study would not proceed to phase III stage. Results: In phase II stage, 60 pts were randomly assigned to treatment group, and 59 to control group. As of Nov 4, 2022, the last randomised pt underwent curatively surgical resection and pathological evaluation. The median age was 58 years (range, 21-75). 101(84.9%) were male, and 96 (80.7%) had HBV infection. In treatment group, 58 pts received neoadjuvant therapy, 52 completed 2 cycles of preoperative therapy and proceeded with planned resection. Surgery was aborted for 6 pts: 3 refused surgery, 2 deaths (1 for tumor rupture of HCC, 1 for immune related hepatitis), and 1 had protocol deviation. The MPR rates in the ITT population were 40% (24/60). Among them, 10% pts (6/60) had ≤5% surviving tumor cells in tumor bed. The MPR rate in pts who had surgical resection were 46.2% (24/52). 19.3% pts experienced ≥3 grade TRAEs, the most common of which were AST increased (5.3%), hypertension (5.3%), and ALT increased (3.5%). Conclusions: The phase II stage of the study did not meet the stopping criteria. Neoadjuvant camrelizumab plus apatinib therapy exhibits promising pathological response in HCC pts at intermediate-high risk of recurrence, with a tolerable safety profile. The phase III stage of the study is currently ongoing. Clinical trial information: NCT04521153. Research Sponsor: Shanghai shenkang hospital development center; Jiangsu Hengrui Pharmaceuticals Co., Ltd.
Robotic and laparoscopic surgery versus open surgery for perihilar cholangiocarcinoma: A meta-analysis.

Laynara Vitória Da Silva Vieira, Mee Joo Kang, Marina Marangoni Roschel, Alana Bruna Krug, Luana Dornelas, Monique Vilela Gomes, Camile Fernanda Squisatti, Yasmin Alves Peterson, Beatriz Meneses, Maria Eduarda Rodrigues Peixoto, Maria Eduarda Cavalcanti Souza, Luiza Carvalho, Vitória Donadoni Costa, Joao Miguel Rabelschini, Carolina Furtado de Oliveira, Isabela Rutkowski, Beatriz Meyer de Souza, Marcella Eduarda de Aguiar Tavares, Heloisa Griese Luciano Santos; Federal University of Piaui, Teresina, Brazil; National Cancer Center South Korea, Seoul, South Korea; Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; Federal University of Santa Catarina, Florianópolis, Brazil; Faculdade De Ciencias Medicas Da Santa Casa De Sao Paulo, São Paulo, Brazil; Federal University of Piaui, Picos, Brazil; University of Minas Gerais, Belo Horizonte, Brazil; University of Marília, Marília -SP, Brazil; Universidade Franciscana-UFN- Santa Maria-RS, Santa Maria, Brazil; Centro Universitário Estácio de Ribeirão Preto, Ribeirão Preto, Brazil; Faculdade Pernambucana de Saude, Recife, Brazil; University of Grande Rio, Rio De Janeiro, Brazil

Background: Robotic and laparoscopic surgeries provide a new approach for patients with perihilar cholangiocarcinoma (pCCA). However, whether it can achieve similar outcomes to traditional open surgery (OS) remains controversial. Therefore, to compare the outcomes of laparoscopic/robotic surgery with open surgery and investigate the efficiency for Klatskin tumors further, we systematically summarized the currently available data and performed a meta-analysis. Methods: A systematic review and meta-analysis were conducted to examine the most recent studies on the topic. The search was updated to January 15, 2023, and was performed on PubMed, LILACS, and Embase. The inclusion criteria were case cohort comparing two arms: robotic or laparoscopic and open surgery for pCCA, based in PICOS principle, while the exclusion criteria were review, letter, and articles with incomplete data. All the included literature was evaluated for quality and risk of bias using the Joanna Briggs Institute’s critical appraisal tool and the data were extracted and entered into an Excel spreadsheet by two authors. The data was then analyzed using Review Manager 5.4 applying Odds Ratio and Mean Difference. The study protocol was registered in PROSPERO (CRD42023388478) and was conducted following the PRISMA 2020 checklist. Results: A total of 1133 patients were included in the study (411 laparoscopic/robotic, 722 open surgeries), 15 retrospective cohort were used in the meta-analysis. The meta-analysis revealed that laparoscopic surgery resulted in less blood loss (Mean difference -77.87; 95% CI = -89.97, -67.78; p < 0.00001, I²= 84%), shorter hospital stay (Mean difference -3.25; 95% CI = -4.83, -1.67; p < 0.00001, I²= 79%) but longer operation time (Mean difference 53.95; 95% CI = 48.09, 59.81; p < 0.00001, I²= 86%). The mortality rate was not significantly different between the two groups (odds ratio = 0.82; 95% CI = 0.47 a 1.42; p = 0.48; I²= 0%). Both surgeries showed similar results for age (Mean difference 1.71; 95% CI = -0.62, 4.03; p =0.15, I²= 53%), bilirubin (Mean difference -43.45; 95% CI = -77.11, -9.79; p< 0.01, I²= 0%), BMI (Mean difference 0.25; 95% CI = -0.24, 0.74; p = 0.31, I²= 0%), and tumor diameter (mean difference -0.06; 95% CI = -0.52, 0.40; p =0.80, I²= 0%). Conclusions: The limitations of the study evidence are due to the small number of patients included in each article. Concerning blood loss and hospital stay, minimally invasive surgery offers better results. However, open surgery still has a shorter operating time. Both surgeries had similar results in mortality. Minimally invasive surgery is as safe as open surgery for pCCA resection. Research Sponsor: None.
Development and validation of a non-invasive cfDNA targeted sequencing assay for early-stage hepatocellular carcinoma detection using cfDNA methylation and fragmentomics.

Rui Liu, De-Zhen Guo, Ao Huang, Cheng-Cheng Ma, Min-Jie Xu, Yi-Ying Liu, Ming-Yang Su, Hua Chen, Yun-Zhi Zhang, Qi-Ye He, Zhi-Xi Su, Xin-Rong Yang, Jia Fan, Jian Zhou; Singlera Genomics Ltd., Shanghai, China; Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University; Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education, Shanghai, China; Liver Cancer Institute, Zhongshan Hospital, and Key Laboratory of Carcinogenesis and Cancer Invasion (Ministry of Education), Fudan University, Shanghai, China

Background: Hepatocellular carcinoma (HCC) is one of the most common cancers in China, and one of the leading causes of cancer-related deaths in the country. With a 5-year survival rate of only 15-20%, early detection is crucial to improve the treatment and survival of HCC patients. Currently, alpha-fetoprotein (AFP) is commonly used as a serum marker for HCC, but it is not a sufficiently specific and can cause false positive readings due to elevated levels caused by other liver conditions. An alternative method is to use circulating free DNA (cfDNA) released by tumor cells as cancer-screening targets, which has been shown to be a more sensitive and specific biomarkers for HCC detection. This study aims to develop a non-invasive screening assay based on cfDNA features to improve the detection of early-stage HCC.

Methods: Candidate methylation markers for HCC detection were collected and evaluated using GEO, TCGA and in-house datasets, 1601 of which were incorporated into a targeted sequencing panel named HcSeer. Multiple types of cfDNA features were constructed from the sequencing data, which included methylation-related features such as methylation haplotype blocks (MHBs) and methylated haplotype fraction (MHF), and fragmentomics features such as end motif and CNV. For model building, Cancer and healthy plasma samples were randomly divided into a training and a testing set at a 2:1 ratio. A two-step deep neural network model was built to classify HCC using selected features of both types. Results: We previously enrolled a total of 401 plasma samples (200 healthy, 201 HCC) for model construction and the performance of the HcSeer model have been documented. An independent validation cohort of 421 plasma samples (280 healthy, 141 HCC) was currently collected from different centers. In this independent validation, the HcSeer model achieved an AUC of 0.98 with a sensitivity of 96.5% at a specificity of 96.4%. Importantly, HcSeer maintained a high sensitivity for HCC across all stages: 94.3%, 96%, 100% and 100% for stage I – IV cases, respectively. When compared to AFP, HcSeer achieved a significantly higher sensitivity of 94% than AFP’s 55% in 137 HCC cases having AFP level tested. When AFP level was combined with the HcSeer model, the sensitivity for HCC further increased to 96%. Conclusions: This study demonstrated that the DNA methylation and fragmentomics patterns of cfDNA can accurately distinguish HCC and healthy plasma samples, particularly in the early stages of HCC. The combination of the HcSeer and AFP further improved the accuracy of the prediction. Although this study was limited in sample size, it clearly showed the potential of the HcSeer assay for accurate HCC detection in blood. Research Sponsor: National Key Research and Development Program of China (2019YFC1315800).
Neoadjuvant immunotherapy with ipilimumab plus nivolumab and radiologically and pathologically quantifiable responses through modulation of the tumour microenvironment in resectable hepatocellular carcinoma.

Antonio D’Alessio, Madhava Pai, Duncan Spalding, Robert D. Goldin, Bernhard Scheiner, James Korolewicz, Claudia A.M. Fulgenzi, Caroline Ward, Vincent Yip, Sarah Slater, Ayse Akarca, Mikael Sodergren, Paul Tait, Nagy A. Habib, Robert Thomas, Alessio Cortellini, Teresa Marafioti, Julian R. Marchesi, Rohini Sharma, David J. James Pinato; Imperial College, London, United Kingdom; Imperial College London, London, United Kingdom; Imperial College, St Mary’s Campus, London, United Kingdom; Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; Imperial College Healthcare NHS Trust, London, United Kingdom; Barts and The London HPB Centre, The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; Barts Health, London, United Kingdom; UCL, London, United Kingdom; Imperial NHS Trust, London, United Kingdom; Imperial College NHS Trust, London, United Kingdom; Division of Surgery and Cancer, Imperial College London, United Kingdom; University College Hospital-London, London, United Kingdom; Imperial College London, Cardiff, United Kingdom

Background: Liver resection (LR) is a potentially curative option for early-stage hepatocellular carcinoma (HCC), and immune checkpoint inhibitors (ICI) are being investigated in the perioperative setting to improve long-term relapse rates and survival outcomes. Methods: PRIME-HCC is a phase Ib study testing nivolumab (3 mg/kg, day 1 and day 22) plus ipilimumab (1 mg/kg, day 1 only) (N+I) prior to LR in resectable HCC. Primary endpoint was safety, while secondary endpoints included radiological response (per RECIST v1.1) and pathological response on resection specimens (ReS). Translational endpoints encompassed analysis of tissue samples with multiplex immunohistochemistry (MIHC) and gut microbiota profiling with high-throughput sequencing and their correlation with response. Results: As of 7th of February 2023, 25 patients (pts) were enrolled, all Child-Pugh A, mostly male (n=18, 72%), with cirrhosis (n=13, 52%), and viral hepatitis (44%, 4 HBV and 7 HCV). Any-grade adverse events (AEs) occurred in 88% pts (n=22), of which 24% (n=6) grade (G) 3. No G4-5 AEs were recorded. Any-grade treatment-related (tr)AEs were reported by 72% pts (n=18), including 8% G3 trAEs (n=1 ALT/AST elevation and n=1 dyspnea). After a median follow-up of 14.5 months (95% CI 7.0-22.0), 21 pts were assessed for radiological response and underwent surgery. Median time from treatment start to LR was 2.4 months (interquartile range 2.2-2.7). LR was delayed in 1 pt (4.8%) because of G2 hypothyroidism but occurred uneventfully. Objective response rate was 29% (n=5 partial responses, n=1 complete response [CR]); disease control rate was 95% (n=20), with 1 progressor having a mixed HCC/cholangiocarcinoma. Major pathological response (MPR), defined as ≥70% tumour regression, was observed in 56% (n=9) of the pathologically evaluable ReS (n=16), with 38% pathological CR (n=6). In the MIHC analyses, pretreatment biopsies of MPR pts were significantly enriched in peritumoral CD4+ and CD8+ cells, with no intratumoral difference. When comparing baseline biopsies and ReS, MPR pts had a significant decrease of intratumoral FOXP3+/CD4+ regulatory T cells (Tregs), while peritumoral Tregs increased significantly in non-MPR ReS. In baseline stool samples, α and β diversity did not differ across responders (R) and non-responders (NR), nor it changed after ICI. However, pre-treatment stool samples of NR pts were significantly enriched in Alistipes and Colinsella genera. Conclusions: Neoadjuvant N+I is feasible and tolerable for early-stage HCC, with promising radiological and pathological response rates. Study of tissue and gut microbiota highlights tumor and host-related changes. Immune infiltrate and gut microbiota composition lend themselves as predictors of anti-tumour efficacy of N+I combination. Clinical trial information: NCT03682276. Research Sponsor: Funder: Bristol Myers Squibb.; Cancer Research UK (RCCPDB- Nov21/100008); Associazione Italiana per la Ricerca sul Cancro, Institute of Hepatology, Wellcome Trust Strategic Fund (PS3416), the Cancer Treatment and Research Trust (CTRT); Infrastructural support by the Cancer Research UK Imperial Centre and the NIHR Imperial Biomedical Research Centre.
The efficacy of radical hepatectomy versus stereotactic body radiotherapy for primary hepatocellular carcinoma: A propensity score matching analysis.

Yulin Hu, Feng-Ming Spring Kong, Ren Ji; Shenzhen University, Shenzhen, Guangdong, China; Department of Clinical Oncology, University of Hong Kong, Hong Kong, China; Division of Hepatobiliary & Pancreatic Surgery, Department of Surgery, The University of Hong Kong-Shenzhen Hospital, Shenzhen, Guangdong, China

Background: Recent international guidelines have included stereotactic body radiotherapy (SBRT) outstanding tumor control as a treatment option for hepatocellular carcinoma (HCC) in several settings. However, data evaluating surgery and SBRT are limited, and results published were controversial. The retrospective study aims to compare the efficacy of hepatectomy and SBRT for HCC.

Methods: The study population started with patients in databases of primary HCC, treated with curative hepatectomy or SBRT, regardless of tumor number, tumor size, cirrhosis and portal vein thrombosis. Patients with prior cancer treatment other than transarterial chemoembolization were excluded. In order to reduce the potential confounding effect of treatment and selection bias, 3-to-1 propensity score models were constructed based on each patient’s estimated propensity score. The variables significant for overall survival were considered for the match, including age, sex, Child-Pugh score, ECOG performance status score, maximum diameter, BCLC stage, prothrombin time, total bilirubin, albumin, and white blood cell. Overall survival and progression-free survival were compared.

Results: A total of 174 patients, 154 in hepatectomy group and 20 in SBRT group, were analyzed. 125 men and 29 women, mean 56.2 years of age, in hepatectomy group. 12 men and 8 women, mean 70.5 years of age, in SBRT group. ECOG was a significant favorable factor for overall survival. Maximum diameter, portal vein embolization, aspartate transferase and albumin was significant favorable factors for disease-free survival of patients with primary hepatocellular carcinomas. Before PSM, patients in the hepatectomy group tended to be younger, had better performance status, less cirrhosis, less tumor number and had better hepatic function than those in the SBRT group (P < .05). The 3-year overall survival rate and median progression-free survival time for the surgical resection and SBRT groups were 77.9% vs 35.4 (P = .003) and 30 vs 20 month (P = .486), respectively. After PSM, 80 patients, 60 in hepatectomy group and 20 in SBRT group, were analyzed. The 3-year overall survival rate and median progression-free survival time for the surgical resection and SBRT groups were 71.9% vs 56.6 (P = .92) and 17 vs 26 month (P = .656), respectively. The patients of hepatectomy group had less cirrhosis, better liver function and less tumor number than those in 20 with SBRT.

Conclusions: For primary HCC, regardless of tumor size and tumor number, stereotactic body radiotherapy can provide similar result on overall survival and tumor control compared to hepatectomy. Stereotactic body radiotherapy can also be less invasive and provide less inpatient time. So stereotactic body radiotherapy can be a effective treatment for patients with primary HCC. Research Sponsor: None.

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Racial disparities in the outcomes of liver transplantation in the treatment of hepatocellular carcinoma.

Syeda Ashna Fatima Kamal, Sindhu Vikash, Haris Sohail, Yassine Kilani, Fnu Vikash; Springfield Memorial Hospital/Southern University of Illinois, Springfield, IL; Jacobi Medical Center/Albert Einstein College of Medicine, NY, NY; Lincoln Medical Center, New York, NY; Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY

Background: According to the National Comprehensive Cancer Network (NCCN), liver transplantation (LT) is currently the treatment of choice for patients with early hepatocellular carcinoma (HCC). A retrospective study in 2016 showed a difference in mortality among races in patients undergoing treatment for HCC. Our study is the first to compare the outcomes of mortality, morbidity and hospital utilization of HCC patients undergoing LT among races in the US.

Methods: This is a retrospective longitudinal study of patients with a primary diagnosis of HCC. We retrieved data from the Nationwide Inpatient Sample (NIS) databases from the years 2016 to 2020 using ICD-10 codes. Multivariate regression analysis was applied to compare the outcomes in races, adjusted for patient and hospital confounders. A T-Test and Chi Square test were performed to compare baseline characteristics. We used STATA Version 17.0 Software for analysis. The p-value was set at p < 0.05 for statistical significance.

Results: Among a total of 112,110 adults with HCC, 2.8% (n=3,150) underwent LT. Blacks had lower rates of LT. Blacks and Hispanics were found to have a lower income (p=0.000). No difference in the Charlson Comorbidity index was noted among races (p=0.5519), however, Blacks had more smokers (p=0.0149). Hispanics had a significant increase in THC compared to Whites (coefficient: 102,058 US Dollars, p=0.033, CI95%: -109,404 - 119,787), with no difference in the length of stay among races. Blacks had higher rates of mortality (p=0.004), acute kidney injury (AKI) (p=0.001), and similar rates of transplant complications.

Conclusions: Our study showed that while Blacks have lower rates of LT, they have a higher rate of mortality and morbidity following LT. Large scale studies are necessary to help determine factors associated with these findings. Research Sponsor: None.
ACTION-1 phase Ib/3 trial of RYZ101 in somatostatin receptor subtype 2–expressing (SSTR2+) gastroenteropancreatic neuroendocrine tumors (GEP-NET) progressing after 177Lu somatostatin analogue (SSA) therapy: Initial safety analysis.

Michael Morris, Gary A. Ulaner, Daniel M. Halperin, Jonathan R. Strosberg, Samuel H. Mehr, Daneng Li, Heloisa P. Soares, Lowell Brian Anthony, Sandy Diana Kotiah, Heather Jacene, Marianne E. Pavel, Pamela L. Kunz, Denis Vasconcelos Ferreira, Joanne Li, Kimberly Ma, Jessica Rearden, Susan Moran, Thomas A. Hope, Simron Singh; Advanced Molecular Imaging and Therapy, Glen Burnie, MD; Hoag Family Cancer Institute and University of Southern California, Newport Beach and Los Angeles, CA; MD Anderson Cancer Center, Houston, TX; Moffitt Cancer Center and Research Institute, Tampa, FL; Nebraska Cancer Specialists, Omaha, NE; City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA; Hunstman Cancer Hospital, University of Utah, Salt Lake City, UT; University of Kentucky, Markey Cancer Center, Department of Medical Oncology, Lexington, KY; Mercy Medical Center, Baltimore, MD; Dana-Farber Cancer Institute, Boston, MA; Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany; Yale University, New Haven, CT; RayzeBio, Inc., San Diego, CA; University of California, San Francisco, San Francisco, CA; University of Toronto, Odette Cancer Center at Sunnybrook Health Sciences Center, Toronto, ON, Canada

Background: RYZ101 (225Ac-DOTATATE) is a first-in-class, highly potent alpha-emitting radiopharmaceutical in development for treating SSTR2+ solid tumors. Alpha-particles (as emitted by 225Ac) have a shorter path length (40–100 μm) and higher linear energy transfer (80–100 keV/μm) than beta-particles, causing more frequent double-strand DNA breaks and potentially higher cancer cell kill rates and less damage to healthy tissues. ACTION-1 (NCT05477576) is a 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 in patients (pts) with advanced well-differentiated SSTR+ GEP-NETs progressing after 177Lu-SSA therapy. Part 1 (phase 1b) aims to determine safety, pharmacokinetics, and recommended phase 3 dose (RP3D) of RYZ101. Methods: Part 1 is an uncontrolled dose de-escalation study with a Bayesian optimal interval design. Escalation (0.197) and de-escalation (0.298) boundaries based on a target dose-limiting toxicity (DLT) rate of 25% were applied. Pts received RYZ101 IV every 8w for up to 4 cycles. Planned dose levels (n=6/level): Level 0 (starting dose), 120 kBq/kg (3.2 mCi/kg); if necessary, Level –1, 90 kBq/kg (2.4 mCi/kg); Level –2, 60 kBq/kg (1.6 mCi/kg). No dose escalation above starting dose was permitted. DLT was assessed for 56d after the first RYZ101 treatment. Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE v5.0. Dose de-escalation decisions and safety data review were overseen by a Data Review Committee. Data cut-off: 26 Oct 2022. Results: At data cut-off, 9 pts had received RYZ101 at 120 kBq/kg (median dose 8.9 MBq); 7 pts were DLT-evaluable. No DLTs occurred and no dose de-escalation steps were implemented. Baseline characteristics: median age 70y; male (n=6)/female (n=3); ECOG PS 0 (n=4)/1 (n=5); median disease duration 6.9y; primary tumor site GI (n=6)/pancreas (n=3). A safety summary is shown. No treatment-related serious AEs were observed. TEAE requiring dose reductions occurred in 2 pts (Grade 2 platelet count decreased, n=1; Grade 2 thrombocytopenia, n=1). Grade 3 or 4 TEAEs occurred in 3 pts (lymphocyte count decreased, n=2; skin infection, n=1; weight decreased, n=1). One serious adverse event (skin infection) was unrelated to treatment. Conclusions: RYZ101 was well tolerated at 120 kBq/kg, which was declared the RP3D. Part 2 (Phase 3) will commence after Part 1 and will compare RYZ101 at the RP3D with standard of care in pts with advanced SSTR2+ GEP-NETs with disease progression following prior 177Lu-labeled SSAs. Clinical trial information: NCT05477576. Research Sponsor: RayzeBio.
Novel use of alternate (Alt) response (Rp) criteria (Cr) for early prediction of outcomes in pancreatic (P) neuroendocrine tumors (NETs): Utilizing banked imaging data from the ECOG-ACRIN E2211 study.

Namrata Vijayvergia, Elizabeth A. Handorf, Pamela L. Kunz, Emel Alkim, Lauren M.B. Burke, Paul J. Catalano, Noah Graham, Laura Levin, Weier Li, Caitlin R. Meeker, Daniel L Rubin, Anush Narasimhan Sridharan, Peter J. O’Dwyer, Terence Z. Wong, Jordan Anaokar; Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA; Yale Cancer Center, New Haven, CT; Stanford University, Stanford, CA; University of North Carolina at Chapel Hill, Chapel Hill, NC; Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; University of Pennsylvania Department of Medicine, Philadelphia, PA; Duke Cancer Institute, Durham, NC

Background: The evaluation of treatment (Tx) Rp in NETs using CT/MRI scans can be difficult. Previous studies, including the E2211, have shown improved progression-free survival (PFS) but no significant difference in Rp as measured by RECIST 1.1 (R1.1) Cr. Thus, making it difficult to determine Tx effectiveness with short-term imaging, further complicated by differences in imaging protocols and inter-reader variability. Incorporating tumor density, using smaller threshold changes in tumor size, and novel quantitative features may be more sensitive and precise than R1.1 (e.g. CHOI in GIST) but they have not been studied for NETs. Methods: Banked CT images from the E2211 trial were repurposed to study novel Cr. Three radiologists provided a R1.1 assessment. Density and radiomic features were calculated from a 2D region of interest in the portal venous phase (as per CHOI Cr). Patients were classified as responders (PR), stable disease (SD), or progressive disease (PD) based on R1.1 and CHOI and compared with PFS to determine the best predictor. Radiomic features were analyzed using pyradiomics. Wilcoxon tests were used to compare scan quality by center type, agreement was measured using Cohen’s Kappa, and predictive value was quantified using the c-statistic and AUC for time-varying outcomes. Results: 67 patients had their scans repurposed for the study. Inter-reader agreement for overall imaging studies was fair, with only 5 of 9 PD cases noted by reviewer 1 being agreed upon by reviewer 2 (proportional agreement for PD = 0.56) and a Kappa of 0.6 (95% CI 0.41 - 0.79). The CHOI Cr showed improved prediction of PFS compared to R1.1 (12-month AUC 0.75 for CHOI vs 0.69 for R1.1, c-statistic 0.66 vs 0.64, p=0.22), and was able to predict improved PFS for PR versus SD at the first interval scan. This was not seen with R1.1 (table). Radiomics and texture analysis as a potential adjunct to CHOI is being studied and results will be presented. Conclusions: This study using repurposed banked imaging from an NCTN trial, found that there was significant variability in the interpretation of images, and that the R1.1 Cr had a poor correlation with Rp in PNETs. The CHOI Cr emerged as a better alternative as it may have a better correlation with PFS and the ability to predict outcomes at the point of first disease assessment. Importantly, CHOI Cr can be easily applied in clinical practice to inform treatment decisions. Further research is needed to confirm these findings and define the therapeutic importance. Research Sponsor: U.S. National Institutes of Health.

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<th></th>
<th>PFS</th>
<th>AUC 12m</th>
<th>c-statistic</th>
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<tr>
<td><strong>Cr/Pt</strong></td>
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<td></td>
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<tr>
<td>R1.1</td>
<td>19.2 m</td>
<td>23 m</td>
<td>331.240 0.692 0.639</td>
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<tr>
<td>(95% CI 15.1-NA)</td>
<td>(95% CI 12.9-30.1)</td>
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<tr>
<td>CHOI</td>
<td>23 m</td>
<td>11.7 m</td>
<td>334.528 0.751 0.658</td>
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<td>(95% CI 17.5-34.2)</td>
<td>(95% CI 8-35.4)</td>
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*Higher c-statistic, higher AUC, and lower Akaike Information Criterion (AIC) are indicators of better predictive ability and fit.
Prevalence of germline variants in patients with pancreatic neuroendocrine tumors.

Chirayu Mohindroo, Seyda Baydogan, Parul Agarwal, Dan Laheru, Robin Wright, Laura Prakash, Maureen E Mork, Alison Klein, Jess Maxwell, Matthew H. G. Katz, Arrind Dasari, Michael Paul Kim, Jin He, Florencia McAllister, Ana De Jesus-Acosta; Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Clinical Cancer Prevention, University of Texas MD Anderson Cancer Center., Houston, TX; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Clinical Cancer Genetics Program, University of Texas MD Anderson Cancer Center, Houston, TX; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; Department of Surgical Oncology University of Texas at MD Anderson Cancer Center, Houston, TX; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: About 10% of pancreatic neuroendocrine tumors (pNETs) are thought to be related to inherited syndromes, including multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 4 (MEN4), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC). Here, we report the prevalence of pathological/likely pathological germline variants (PV/LPV) in 2 cohorts: 1) High-risk and 2) Unselected. Methods: We retrospectively collected clinical data of patients with biopsy proven pNETs seen at MD Anderson Cancer Center (MDACC) and Johns Hopkins Hospital (JHH). Cohort 1 (high risk cohort) included 132 patients seen at MDACC, who underwent germline testing based on high-risk criteria such as early onset, personal or family history of cancer and syndromic features between 2013-2019. Cohort 2 (unselected cohort) included 106 patients seen at JHH, who underwent germline testing following their diagnosis of pNETs between 2020 to 2022. Results: In the high-risk cohort (n = 132), 33% (n = 44) had PV/LPV, and 17% (n = 22) had a variant of unknown significance (VUS). Amongst the 132 patients, 35% underwent multigene panel testing, 53% had targeted germline testing and 12% had a physician documented outside test diagnosis. The demographics consisted of 52%(n = 69) females, 67% (n = 88) white, 54%(n = 71) had metastatic disease, 58%(n = 76) underwent surgical resection. WHO grading (n = 77) is as follows G1 (39%), G2 (59%), G3 (2%). In the unselected cohort (n = 106), 21% (n = 22) had PV/LPV, 28% (n = 30) had a VUS. Of these, 93% of the patients underwent multigene panel testing. The demographics consisted of 42% (n = 44) females, 67% (n = 88) white, 48% (n = 51) had metastatic disease, 60% (n = 64) underwent surgical resection. WHO grading (n = 93) is as follows G1 (37%), G2 (49%), G3 (14%). Conclusions: PV/LPV are prevalent in patients with sporadic pNET irrespective of high-risk features or family history. While in the high-risk patients there is a higher prevalence, we also identified a 21% prevalence of PV/LPV with universal germline testing in the unselected cohort. In both cohorts, we identified a high number of mutations in the DNA repair pathway not previously described, which could affect subsequent therapies and surveillance for patients and their family members. The findings support upfront universal germline testing in all patients with diagnosis of pNETs. Research Sponsor: None.

<table>
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<tr>
<th>Mutation Type</th>
<th>MDACC (High Risk Cohort)</th>
<th>JHH (Unselected Cohort)</th>
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<tr>
<td>MEN1</td>
<td>56% (n = 25)</td>
<td>36% (n = 8)</td>
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<tr>
<td>DNA Repair pathway</td>
<td>18% (n = 9)</td>
<td>40% (n = 9)</td>
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<tr>
<td>VHL</td>
<td>11% (n = 5)</td>
<td>9% (n = 1)</td>
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<tr>
<td>Colon cancer related genes</td>
<td>11% (n = 5)</td>
<td>9% (n = 2)</td>
</tr>
<tr>
<td>Others</td>
<td>2% (n = 1)</td>
<td>9% (n = 2)</td>
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Safety and clinical activity of oleclumab (O) ± durvalumab (D) + chemotherapy (CT) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC): A phase 1b/2 randomized study.

Andrew L. Coveler, Matthew Reilley, Mark Zalupski, Teresa Macarulla, Christos Fountzilas, Eduardo Castanon Alvarez, Adnan Nagrial, Natálie Vołodymyrivna Uboha, Sophia Frentzas, Michael J. Overman, Anne M. Noonan, Wells A. Messersmith, Nick Pavlakis, Niharika B. Mettu, Paul Smith, Elina Murtomaki, Veronique Bragulat, Zachary A. Cooper, Rakesh Kumar, David Spigel; Fred Hutchinson Cancer Center, Seattle, WA; University of Virginia Comprehensive Cancer Center, Charlottesville, VA; University of Michigan Health System, Ann Arbor, MI; Hospital Universitari Vall d’Hebron, Barcelona, Spain; Roswell Park Cancer Institute, Buffalo, NY; Clínica Universidad de Navarra, Madrid, Spain; Blacktown Hospital, Sydney, Australia; University of Wisconsin Carbone Cancer Center, Madison, WI; Monash Health-Monash Medical Centre, Clayton, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; The Ohio State University Comprehensive Cancer Center, Columbus, OH; University of Colorado, Denver, CO; Northern Sydney Cancer Centre - Royal North Shore Hospital, Sydney, Australia; Duke University Medical Center, Durham, NC; On behalf of AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Gaithersburg, MD; Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN

Background: In a phase 1 study, the anti-CD73 monoclonal antibody (mAb) O plus the anti-PD-L1 mAb D showed antitumor activity and manageable safety in previously treated pts with advanced PDAC (Overman et al, J Clin Oncol 2018;36(suppl 15):abs 4123). Here we report a multicenter, open-label study of O ± D + CT in pts with mPDAC. Methods: Pts were ≥18 years old with ECOG PS 0–1. Part 1 was a dose escalation phase: in Cohort A, previously untreated (1L) pts received O 1500 or 3000 mg IV Q2W for 4 doses then Q4W + D 1500 mg IV Q4W, with Q4W gemcitabine and nab-paclitaxel (GnP). In Cohort B, pts with previous G-based CT (2L) received O 1500 or 3000 mg Q2W for 4 doses then Q4W + D 1500 mg Q4W, with Q4W mFOLFOX. The primary objective for Part 1 was safety and tolerability; secondary objectives included antitumor activity and pharmacokinetics (PK). Part 2 was an expansion phase in which pts were stratified by high/low tumoral CD73 expression by IHC. In Cohort A, 1L pts were randomized 1:1:1 to GnP alone (Arm A1), O + GnP (Arm A2) or O + D + GnP (Arm A3). O was given at the recommended phase 2 dose, 3000 mg. Cohort B did not proceed to dose expansion due to emerging therapies in 2L PDAC pts. The primary endpoint for Part 2 was investigator-assessed objective response rate (ORR) by RECIST v1.1; secondary included PFS, OS, safety, PK and antidrug antibody data. Results: As of November 11, 2022, 25 pts were treated in Part 1 (Cohort A, n=14; Cohort B, n=11), and 170 pts were treated in Part 2 (Arm A1, n=62; Arm A2, n=38; Arm A3, n=70). In Part 1, dose-limiting toxicities occurred in 1 pt (Cohort B, O 3000 mg: Gr 3 nausea and Gr 3 localized edema). Safety was generally similar in Parts 1 and 2. In Part 2, Gr ≥3 treatment-emergent adverse events (TEAEs) occurred in 85.5%, 89.5% and 90.0% of pts in Arms A1, A2 and A3 respectively, most commonly neutropenia (22.6%, 34.2% and 17.1%). In Part 2, TEAEs led to discontinuation in 11.3%, 23.7% and 24.3% of pts respectively. In Part 2, ORR was similar across Arms with a trend toward longer PFS and OS in Arm 3 vs Arm 1. There was a trend toward greater clinical benefit in pts with high CD73 expression when comparing Arm A3 vs Arm A1. Conclusions: O + D + GnP had similar safety and a trend toward improved outcomes compared to GnP. Clinical trial information: NCT03611556. Research Sponsor: AstraZeneca.

Part 2 efficacy summary.

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<tr>
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<tr>
<td>ORR, % (95% CI)</td>
<td>29.0 (18.2, 41.9)</td>
<td>21.1 (9.6, 37.3)</td>
<td>32.9 (22.7, 45.1)</td>
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<tr>
<td>ORR difference, % (95% CI), p value</td>
<td>0.0276, 0.860</td>
<td>-0.003, 0.471</td>
<td>0.059, 0.361, 0.051</td>
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<td>DCR 12w, % (95% CI)</td>
<td>66.1 (53.0, 77.7)</td>
<td>75.7 (62.9, 86.6)</td>
<td>75.7 (64.0, 86.2)</td>
</tr>
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<td>mPFS, mo (95% CI)</td>
<td>6.7 (5.0, 9.4)</td>
<td>8.0 (6.0, 10.0)</td>
<td>9.5 (7.5, 10.6)</td>
</tr>
<tr>
<td>PFS hazard ratio (95% CI)</td>
<td>0.719 (0.489, 1.05)</td>
<td>0.750 (0.498, 1.131)</td>
<td></td>
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<tr>
<td>mOS, mo (95% CI)</td>
<td>10.8 (8.2, 13.3)</td>
<td>11.0 (9.0, 13.3)</td>
<td>11.3 (10.3, 12.4)</td>
</tr>
</tbody>
</table>
Retrospective evaluation of the value of DNA damage repair gene signature in response to platinum-based chemotherapy in advanced pancreatic ductal adenocarcinoma.

Tian Tian, Carles Fabregat Franco, Gloria Castillo, Florian Castet, Helena Verdaguer, Daniel Lopez Valbuena, Ana Carmona-Alonso, Ana Vivancos, Teresa Macarulla; Preclinical and Translational Research Program, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall d’Hebron Institute of Oncology (VHIO), Vall d’Hebron University Hospital, Department of Medical Oncology, Barcelona, Spain; Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; VHIO, Barcelona, Spain; Hospital General de Granollers, Granollers, Spain; Vall d’Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Gastrointestinal and Endocrine Tumor Unit, Vall d’Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d’Hebron, Vall d’Hebron Barcelona Hospital Campus, Barcelona, Spain; Cancer Genomics Group, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall d’Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d’Hebron University Hospital (HUHV), Barcelona, Spain

Background: Mutations affecting DNA Damage Repair (DDR) genes have been associated with clinical benefits from platinum-based chemotherapy (PBC) in ovarian and breast cancer. Mutations of DDR genes, including BRCA1/2, PALB2, ATM, ATR, CHK1, or RAD51, are found in around 15% of pancreatic ductal adenocarcinoma (PDAC). Nevertheless, whether advanced PDAC patients harboring DDR gene mutations could benefit more from PBC has not been well established. In this study, we aimed to compare the prevalence of DDR gene mutations between advanced PDAC patients who benefited from PBC and those who did not. Methods: We retrospectively analyzed samples from patients with advanced PDAC who received PBC at our institution from 2008 to 2022. Patients with partial response or progression-free survival (PFS) > 6 months were considered responders, and those with progression disease as the best response were considered non-responders. Tumor molecular profiling was performed on tumor samples by Next Generation Sequencing (NGS) of DNA. Fisher’s exact test was used to compare DDR genomic alterations in responders vs. non-responders. Overall survival (OS) was defined as the time from the start of PBC to the date of death. PFS was defined as the time between the start of PBC and the first date of documented progression or death, whichever occurs first. Survival outcomes were estimated using Kaplan-Meier curves, and differences were tested using the long-rank test. Results: A total of 132 patients with advanced PDAC treated with PBC were included in this study. The median age at diagnosis was 55 years (range 27-79 years), and 71 (53.79%) patients were male. In this cohort, 88 (66.67%) patients were identified as responders. Tumor molecular profiling showed that among responders, 42 patients (47.7%) had genomic alterations in BRCA1/2 or PALB2, and 10 patients (11.3%) had alterations in other DDR genes. In contrast, only 17 patients (38.64%) showed DDR gene alternations among non-responders. Importantly, mutations in DDR genes are significantly associated with the responder group (OR=2.28; 95% CI 1.03-5.17, p=0.04). In line with these findings, patients with DDR gene mutations showed significantly longer PFS (median PFS 9.95 months) compared with patients without DDR gene mutations (median PFS 6.51 months) (HR=0.57; 95%CI 0.39-0.85; p=0.005). Moreover, significantly longer OS was found in patients with DDR gene mutations (median OS 20.5 months) compared with those without DDR gene mutations (median OS 16.8 months) (HR=0.67; 95%CI 0.45-1; p=0.05). Conclusions: Genomic alterations in DDR genes are significantly associated with the benefit of PBC treatment in advanced PDAC patients. Our results argue in favor of using DDR genes as a decision-making tool for advanced PDAC patient stratification even before the stand-of-care chemotherapies. Research Sponsor: ISCIII.
Genomic characterization of somatic mutations by race and ethnicity in pancreatic cancer defined through AACR project GENIE.

J. Alberto Maldonado, Chin-Hsien Tai, Christine Alewine; Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: KRAS, TP53, SMAD4, and CDKN2A are widely recognized as the most common somatic mutations amongst patients with pancreatic ductal adenocarcinoma (PDAC); however, previous genomic studies have disproportionately included non-Hispanic White (NHW) patients with little to no inclusion of racial and ethnic minorities, particularly non-Hispanic Black (NHB) and Hispanic patients. Additionally, little is known about the distribution of KRAS point mutations in PDAC in specific racial and ethnic groups. Here, we describe somatic mutation differences in a larger and more racially and ethnically representative PDAC cohort than previously characterized. Methods: PDAC mutational data was downloaded from AACR Project GENIE (Genomics Evidence Neoplasia Information Exchange) v13.0, an international data registry of sequenced tumor samples from nearly 150,000 patients, on cBioPortal. PDAC cancer type was identified using OncoTree code. NHW, NHB, Hispanic (of any race), and Asian patients were then selected. Mutational frequency was calculated for all mutations. The primary objective was to compare the mutation frequencies between NHW and other races with respect to the most common mutations. To maximize power, we included any mutation with a frequency $\geq 5.0\%$ where testing for mutation of that gene had been performed in at least 150 patients. Specific point mutations in KRAS were also extracted with stratification for racial and ethnic group. Fisher's Exact Test was used to calculate the statistical significance of the differences in mutation frequency between NHW and minority groups. Results: Patients in the PDAC cohort included 5,292 individuals (NHW N = 4296, 80.7%; NHB N = 264, 5.0%; Hispanic N = 460, 8.7%; Asian N = 299, 5.7%). As compared to the NHW group, NHB patients had higher rates of TP53 (78.7% vs 69.0%, $P = 0.0006$) and PTPRT (5.3% vs 1.8%, $P = 0.0095$) mutations but fewer GNAS (0.4% vs 2.8%, $P = 0.0097$) mutations while Asian patients had higher frequency of ARID1A mutations (13.0% vs 8.8%, $P = 0.024$). KRAS G12D mutation was more prevalent in Hispanic patients (47.0% Hispanic vs 41.1% NHW, $P = 0.0238$), although rate of KRAS mutation overall was the same. Prevalence of KRAS G12C mutation was equivalent amongst all groups with an overall 1.6% frequency. Conclusions: Understanding the genomic landscape of PDAC is critical as we move towards increased use of targeted therapies to treat this disease. In this study, TP53, PTPRT, GNAS, and ARID1A mutations were shown to occur at different frequencies in specific racial and ethnic groups. G12D mutation of KRAS was disproportionally increased in Hispanics. These differences in molecular landscape amongst racial and ethnic groups could contribute to precision medicine strategies used to address this deadly disease. Research Sponsor: NIH Medical Research Scholars Program.
Efficacy and safety of mitazalimab in combination with mFOLFIRINOX in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): An interim analysis of the optimize-1 phase 1b/2 study.

Hans Prenen, Ivan Borbath, Karen Paula Geboes, Philippe Alexandre Cassier, Aurélien Lambert, Emmanuel Mitry, Teresa Macarulla, Julien Taieb, Jean-Frédéric Blanc, Jaime Feliu Batlle, Mercedes Rodríguez Garrote, Roberto A. Pazo Cid, Manuel Valladares-Ayerbes, Karin Nordbladh, Karin Enell Smith, Peter Ellmark, Malin Carlsson, Yago Pico de Coañá, Sumeet Vijay Ambarkhane, Jean-Luc Van Laethem; Center for Oncological Research (CORE), Integrated Personalized and Precision Oncology Network (IPPON), University of Antwerp, Wilrijk, Belgium; Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium; Department of Gastroenterology, Division of Digestive Oncology, Ghent University Hospital, Ghent, Belgium; Centre Léon Bérard, Lyon, France; Institut De Cancérologie De Lorraine, Vandoeuvre Les Nancy, France; Institut Paoli-Calmettes, Marseille, France; Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; Georges Pompidou European Hospital, Paris, France; Hôpital Haut-Lévêque, CHU de Bordeaux, Service Hépato-Gastroentérologie et Oncologie Digestive, Bordeaux, France; Hospital Universitario La Paz, Madrid, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Hospital Universitario Miguel Servet, Zaragoza, Spain; Virgen del Rocío University Hospital, Sevilla, Spain; Alligator Bioscience AB, Lund, Sweden; Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

Background: Mitazalimab is a human CD40 agonistic IgG1 antibody. Targeting CD40 kickstarts the cancer immunity cycle by licensing dendritic cells leading to tumor specific T cell priming and activation. Furthermore, in PDAC CD40 agonists on myeloid cells promote degradation of the desmoplastic tumor stroma, improving influx of T cells and chemotherapeutic agents into the tumor. OPTIMIZE-1 (NCT04888312) is a Phase 1b/2, open label, multicenter study designed to evaluate safety, tolerability, and efficacy of mitazalimab in combination with mFOLFIRINOX (Oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 150 mg/m², 5-FU 2.4 g/m²) in patients (pts) with previously untreated mPDAC. In the first part of the study (phase 1b), 900 µg/kg mitazalimab was selected as the recommended phase 2 dose (RP2D).

Methods: In the first 21 day treatment cycle, mitazalimab was administered IV at RP2D on day 1 and 10 and mFOLFIRINOX infusion started on day 8. In subsequent cycles, treatment followed a 14 day cycle where mitazalimab was always administered 2 days after mFOLFIRINOX. The primary endpoint of this ongoing study is overall response rate (ORR) per RECIST v1.1. Secondary and exploratory endpoints include progression free and overall survival, safety, PK and PD biomarker assessments. Futility was prespecified as ORR ≤30% in pts treated at RP2D, based on historical data with FOLFIRINOX (Conroy, 2011).

Results: As of December 8, 2022, 43 pts with untreated mPDAC were treated with mFOLFIRINOX and 450 µg/kg (N = 5) or 900 µg/kg (N = 38) mitazalimab and evaluated for safety. The most common grade (Gr) ≥3 TEAEs were neutropenia (16%), fatigue (12%) and hypokalemia (12%). Mitazalimab related Gr ≥3 AEs were fatigue in 3 (7.9%) pts, hypokalemia in 2 (5.3%) pts, diarrhea in 1 (2.6%) pt, pneumonia in 1 (2.6%) pt, increased ALT in 1 (2.6%) pt, headache in 1 (2.6%) pt, acute kidney injury in 1 (2.6%) pt. 10 pts (23%) experienced infusion reactions (all Gr 1-2) and 5 (12%) pts discontinued treatment due to TEAEs (pneumonia, gastric obstruction, neuropathy, bacteremia). At cutoff, 23 pts were evaluable for futility. Median follow up was 170 days and median exposure was 163 days. 18 pts (78%) remain on treatment, 6 (26%) beyond the 6 month treatment period. ORR was 52.2% (12 partial responses), an additional 8 pts achieved stable disease, resulting in a 91.3% disease control rate. Combination with mFOLFIRINOX had no impact on mitazalimab PK. The PD biomarker profile was consistent with the mode of action of mitazalimab, including upregulation of MCP-1 and IFN-γ.

Conclusions: Mitazalimab + mFOLFIRINOX is a feasible regimen with a manageable safety profile. Mitazalimab administered at 900 µg/kg in combination with mFOLFIRINOX shows encouraging antitumor activity in mPDAC, meriting continued development. The study passes futility and continues to full accrual. Clinical trial information: NCT04888312. Research Sponsor: Alligator Bioscience AB.
Phase 2 trial of pembrolizumab and olaparib (POLAR) maintenance for patients (pts) with metastatic pancreatic cancer (mPDAC): Two cohorts B non-core homologous recombination deficiency (HRD) and C exceptional response to platinum-therapy.

Wungki Park, Catherine O’Connor, Joanne F. Chou, Carly Schwartz, Anna M. Varghese, Mary Larsen, Fiyinfolu Balogun, Robin Brenner, Kenneth H. Yu, Erin Diguglielmo, Shigeaki Umeda, Elias Karnoub, Fergus Keane, Haochen Zhang, Smita Suhas Joshi, Nadeem Riaz, David Paul Kelsen, Marinela Capanu, Christine A Iacobuzio-Donahue, Eileen Mary O'Reilly; Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Epidemiology & Biostatistics, Memorial Sloan Kettering, New York, NY; MSKCC, New York, NY

**Background:** Maintenance olaparib improves PFS in gBRCA1/2m (core HRD) in mPDAC (Golan, NEJM 2019). Whether other HRD indicators, such as gene mutations other than gBRCA1/2m (non-Core HRD, Cohort B) and exceptional platinum responders (Cohort C, response > 6 months) may benefit from PARPi in mPDAC remains unanswered. We hypothesized that pembrolizumab and olaparib (POLAR) combination may improve outcome by immunogenic cell death. **Methods:** We conducted an open-label, non-randomized, phase 2 trial of POLAR as maintenance therapy for pts with mPDAC whose disease had not progressed for 4 months (m) in Cohort B or 6 m in C. Herein, we report on Cohorts B & C. Eligibility: ECOG 0-1, mPDAC meeting eligibility of B or C. POLAR (Pembrolizumab 200mg IV Q3W+ OLAPaRib 300mg BID) until disease progression or limiting toxicity. Objective response rate (ORR), median PFS (mPFS), median overall survival (mOS), disease control rate (DCR), CA 19-9, cfDNA and baseline HRD mutational signature were analyzed. **Results:** Cohorts B and C enrolled N=15 each. N=25 pts evaluable by RECIST 1.1. Median follow-up 9.9 (1.3-22.8) and 11.3 (5.8-23) m, respectively. Efficacy details are shown. G3-5 AEs related to treatment: 5/14 (36%): 1 diarrhea (7%), 1 hyperglycemia (7%), 2 anemia (14%), 1 lipase increased (7%). Cohort B: 9/15 (60%) ATM, 3 CHEK2, 2 MUTYH, 1 BLM, 1 FANCC. Canonical gene mutations for mPDAC were less common for pts in Cohort B, especially in ATM PA group (n=9) vs C. Median genomic instability score (GIS) was computed and higher 28 (0-38) vs 9 (0-24) in Cohort B vs C, p=0.052. Median tumor mutation burden (TMB) was not different between B and C (3.3 and 4.1). **Conclusions:** Clinical activity of POLAR maintenance observed in select pts in B and C. Although PFS was modest (mPFS of 4m [2.1-5.4] in B + C), an intriguing survival signal (mOS at 14m [10-NR] from first POLAR dose) was seen in select patients without chemotherapy. Extensive correlative analyses underway to evaluate response and resistance (SPORE: 1P50CA257881-01A1). Cohort A (core HRD) actively accruing. Clinical trial information: NCT04666740. Research Sponsor: Merck Sharp & Dohme LLC; Parker Institute for Cancer Immunotherapy; U.S. National Institutes of Health.

<table>
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<th>Cohorts (N)</th>
<th>Cohort B (15)</th>
<th>Cohort C (15)</th>
<th>B and C (30)</th>
<th>ATM (8)</th>
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<td>64 (42-76), 15:15</td>
<td>62 (42-76), 5:4</td>
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<td>De novo stage IV % (N)</td>
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<td>100 (15)</td>
<td>93 (28)</td>
<td>89 (8)</td>
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<td>ORR % (of pts evaluable for RECIST)</td>
<td>0% (11)</td>
<td>13.5% (14)</td>
<td>8% (25)</td>
<td>0% (8)</td>
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<td>DCR %</td>
<td>60.0%</td>
<td>46.5%</td>
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<td>75% (35-97)</td>
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<td>Median PFS (95%CI)</td>
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<td>87.87(20.53)</td>
<td>82.71(25.36)</td>
<td>75.75(36.0)</td>
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<td>0%</td>
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<td>Median GIS (range)</td>
<td>28 (0-38)</td>
<td>9 (0-24)</td>
<td>17 (0-38)</td>
<td>24 (1-30)</td>
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<tr>
<td>Median TMB (range)</td>
<td>3.3 (0-8.14)</td>
<td>4.1 (1.6-8.2)</td>
<td>3.7 (0-8.14)</td>
<td>2.9 (0.8-4.40)</td>
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</table>
Development and evaluation of 5FUCore, OxaliCore, and IrinoCore transcriptomic signatures for predicting response to individual drugs in the FOLFIRINOX regimen: Towards toxicity reduction and personalized chemotherapy in PDAC.

Nicolas Fraunhoffer, Carlos Teyssedou, Patrick Pessaux, Martin Bigonnet, Nelson J. Dusetti, Juan Iovanna; Cancer Research Center of Marseille (CRCM), INSERM, CNRS, Institut Paoli-Calmettes, Aix-Marseille University, Marseille, France; Department of General, Digestive, and Endocrine Surgery, Nouvel Hôpital Civil, Strasbourg, France; Predicting Med, Marseille, France

Background: Recently, we have successfully developed a transcriptomic signature that predicts the response to gemcitabine treatment in patients with localized pancreatic ductal adenocarcinoma (PDAC) (PMID: 36178036) and also in those with metastatic PDAC (PMID: 36496056). This was achieved by using an approach that combined several preclinical PDAC models. The FOLFIRINOX regimen (FFX) consisting of 5-Fluorouracil (5FU), Oxaliplatin, and Irinotecan is the more effective treatment option, but the high toxicity limits its use. In this study, we developed and analyzed three different transcriptomic signatures for the drugs composing FFX separately and evaluated their clinical utility.

Methods: We combined the transcriptomic profile of 14 patients derived xenograft (PDX) and 31 patients derived cell cultures (PDC) with their corresponding chemotherapy response profiles. We developed predictive signatures for 5FU (5FUCore), Oxaliplatin (OxaliCore), and Irinotecan (IrinoCore), as previously reported for the GemCore signature (PMID: 36178036). They were then validated in three independent cohorts of patients: COMPASS (n = 94), Linehan (n = 28), and a new cohort of 87 advanced PDAC patients.

Results: Three ICA components that reflect the chemotherapy response profiles for 5FU, oxaliplatin, and irinotecan were evaluated in the COMPASS cohort to determine their ability to identify sensitive patients in the FFX arm. Patients predicted as sensitive to each drug separately had a median overall survival (OS) of 77.6 (95% CI, 67.9-NR, P = 0.02), 78.7 (95% CI, 57.6-NR, P = 0.002), and 70.4 (95% CI, 57.6-NR, P = 0.02) months for 5FU, oxaliplatin, and irinotecan, respectively. Notably, the model that integrated the group of sensitive patients to two or three drugs had the highest median OS in the COMPASS and Linehan cohorts with a HR of 0.25 (95% CI, 0.11-0.57; P < 0.001) and 0.11 (95% CI, 0.02-0.70; P = 0.019), respectively. Importantly, they also show a better objective response than the other groups (P = 0.009). In the advanced PDAC group, the signatures showed a strong ability to discriminate sensitive patients in the FFX arm with a median OS of 20.1 (95% CI, 2.3-NR, P = 0.006), 13.64 (95% CI, 9.57-NR, P = 0.003), and 15.87 (95% CI, 2.9-NR, P = 0.002) months for 5FU, oxaliplatin, and irinotecan, respectively. Finally, we evaluated the best combination of two drugs in the pooled group. Patients sensitive to both 5FU and oxaliplatin showed the best response with 60% of patients achieving partial response.

Conclusions: The signatures developed provide a tool for predicting responsiveness to the individual therapeutic drugs of the FFX regimen. They may ultimately lead to the development of a personalized strategy for combined chemotherapy regimens, increasing efficacy and reducing toxicity in PDAC. Research Sponsor: Institut Nationale du Cancer, Inca.
A phase 1b/2 study of surufatinib plus camrelizumab, nab-paclitaxel, and S-1 (NASCA) as first-line therapy for metastatic pancreatic adenocarcinoma (mPDAC).

Guang-Hai Dai, Ru Jia, Haiyan Si, Zhi-Kuan Wang, Guo-Chao Deng, Nan Zhang, Fang-Fang Liu, Yue Shi, Yao-Yue Zhang, Yu-Shan Jia, Bei Zhang, Shuang Tong; Senior Department of Oncology, the 5th Medical Center of the PLA General Hospital, Beijing, China; Medical Affairs, 3D Medicines, Shanghai, China

Background: PD-1 blockade combined with anti-angiogenesis such as surufatinib (targeting VEGFR 1-3, FGFR1 and CSF1-R) might change tumor environment thus improve the efficacy in several solid tumors. A phase 1b/2 clinical study was conducted to explore the efficacy and safety of surufatinib combined with camrelizumab (PD-1 antibody), nab-paclitaxel and S-1 (NASCA) as first-line treatment compared with nab-paclitaxel and gemcitabine (AG) in mPDAC.

Methods: In phase 1b, patients (pts) with mPDAC received surufatinib (200mg to 300mg, orally daily), camrelizumab (200mg, I.V., D1, Q3W), nab-paclitaxel (125mg/m², I.V., D1, D8, Q3W) and S-1 (40mg bid, D1-14, Q3W). Phase 2 is a prospective, open-label, randomized (1:1) trial comparing NASCA with AG in the first-line setting. The primary objective was recommended phase 2 dose (RP2D) and overall response rate (ORR) per RECIST v1.1. Tumor tissue samples were collected at diagnosis for miHC to evaluate tumor microenvironment.

Results: Six pts were enrolled in phase 1b and RP2D was determined as surufatinib 200mg. By Jan 10, 2023, 28 pts were enrolled in phase 2 and 27 pts were evaluable for efficacy (14 in NASCA and 13 in AG). The ORR was 55.0% (11/20) (95% CI: 34.2-74.2) in NASCA and 23.1% (3/13) (95% CI: 8.2-50.3) in AG group. Pts receiving NASCA with liver metastases exhibited significant higher ORR than those without liver metastases (90.0% vs 20.0%, p=0.0017). Median progression-free survival was 8.8 months (95% CI: 5.5-12.0) in NASCA and 5.8 months (95% CI: 1.5-10.1) in AG group at the median follow-up of 8.9 months. The most frequent adverse events (AEs) of all grades in pts treated with NASCA were neutropenia (55.0%), hepatotoxicity (45.0%), neuropathy (35.0%) and diarrhea (15.0%). Immune-related AEs were observed in 4 pts (20.0%) with grade 3 hepatotoxicity. Safety was comparable in two groups except for hepatotoxicity and diarrhea. The tissue of 13 pts receiving NASCA were stained for multiple markers of immune cells. CD3+T cells infiltrated most in the tumor core, followed by CD68+CD163- (M1) macrophages, and FOXP3+ T cells. Majority of immune cells and therapeutic biomarkers were expressed at higher levels in the stroma than tumor core. Pts with liver metastases displayed elevated infiltration of tumoral FOXP3+ T cells (p=0.031), PD-L1+CD68+ macrophages (p=0.014), and decreased density of stromal CD8+ T cells (p=0.064) than pts without liver metastases. In pts with liver metastases, responders displayed a higher proportion of stromal PD-L1+ cells than non-responders (p=0.036). Conclusions: Preliminary results showed that NASCA regimen presented higher clinical activity than the standard AG treatment, especially in pts with liver metastases, with a manageable safety profile. This trial is ongoing and NASCA regimen deserves further exploration in mPDAC. Clinical trial information: NCT05218889. Research Sponsor: HUTCHISON CHINA MEDITECH LTD.
A phase II study of nivolumab and ipilimumab with radiation therapy in patients with metastatic, microsatellite stable pancreatic adenocarcinoma.

Julie L. Koenig, Leon Pappas, Beow Y. Yeap, Jeffrey William Clark, Colin D. Weekes, Jill N. Allen, Lawrence Scott Blaszkowsky, David P. Ryan, James M. Cleary, Joseph Douglas Mancias, Benjamin L. Schlechter, Sarah Elizabeth Slater, Jennifer Yon-Li Wo, Hannah Johnson Roberts, Sofia Von Fedak, Nicole Carzo, Lorraine C. Drapek, Arnav Mehta, Theodore S. Hong, Aparna Raj Parikh; Harvard Radiation Oncology Program, Boston, MA; Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Department of Radiation Oncology, Brigham and Women’s Hospital, Boston, MA; Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Metastatic pancreatic ductal adenocarcinoma (PDAC) is incurable for most patients. While immune checkpoint inhibitors (ICIs) have limited efficacy in microsatellite stable (MSS) tumors, radiation therapy (RT) may promote responsiveness to ICIs. In our phase 2 trial (NCT03104439), 25 patients with metastatic MSS PDAC were enrolled to receive ipilimumab and nivolumab with RT (24 Gy/3 fractions) starting on C2D1. The disease control rate (DCR) was 20% (5/25) and overall response rate (ORR) was 12% (3/25). In 17 patients who received RT (32% dropout rate), DCR was 29% (5/17) and ORR was 18% (3/17). To confirm this signal and address dropout prior to RT, we conducted a phase 2 study of nivolumab and ipilimumab with RT moved to C1D1. Methods: In this open-label, single-arm, phase 2 study (NCT04361162), eligible patients had histologically confirmed metastatic MSS PDAC, ECOG PS 0-2, and progressed on at least one line of chemotherapy. Treatment consisted of ipilimumab 1 mg/kg q6weeks for the first 4 cycles, nivolumab 240 mg q2weeks on a 6-week cycle, and RT (24 Gy/3 fractions) to a single site starting on C1D1. Treatment continued until disease progression, discontinuation, or withdrawal. The primary endpoint was RECIST 1.1 ORR by centrally reviewed imaging q3months. Secondary endpoints included DCR, PFS, OS, and safety. 30 patients were enrolled in a single-stage design for intention-to-treat (ITT) analysis of patients receiving at least one dose of study treatment. The per protocol analysis included patients who completed C1D1. The treatment regimen was considered to have promising activity if at least 3 of 30 patients had an objective response, providing 85% power to reject 5% ORR in favor of 15% ORR at a significance level of 20%. Results: We enrolled 30 patients (median age 68 years [range 52-80], 60% male, 90% white, 97% ECOG PS 0-1, median 3 [range 2-6] prior lines of chemotherapy) from 05/2020 to 11/2021. ITT ORR was 3% (1/30; 95% CI, 0-17%), DCR was 10% (3/30; 95% CI, 2-27%), median PFS was 2.2 months (95% CI, 1.5-2.6), and median OS was 2.8 months (95% CI, 2.1-5.2). In the per protocol analysis, ORR was 4% (1/28; 95% CI, 0-18%), DCR was 11% (3/28; 95% CI, 2-28%), PFS was 2.3 months (range, 1.6-2.7), and OS was 2.9 months (range, 2.2-5.5). One patient enrolled in hospice after 1 month, had a complete response at 13 months, and is alive at 21 months. 7 patients had grade 3-4 treatment-related serious adverse events, including lymphopenia (grade 4 in 1 patient), neutropenia, fatigue, muscle weakness, ALT/AST increase, hepatobiliary dysfunction, acute kidney injury, hyperglycemia, and hypokalemia. Conclusions: The treatment regimen of ipilimumab and nivolumab with RT did not meet the pre-specified criteria for promising activity in metastatic MSS PDAC. Further correlative analyses of the patient with a complete response and evaluation of in-field responses are ongoing. Clinical trial information: NCT04361162. Research Sponsor: Bristol Myers Squibb.
Correlation of comprehensive molecular mapping of pancreatic ductal adenocarcinoma with XPO1 mRNA expression levels to potential clinical targets.

Andreas Seeber, Rebecca Gruber, Florian Kocher, Kai Zimmer, Alberto Puccini, Harris Benjamin Krause, Daniel Neureiter, Eckhard Kliest, Stefan Salcher, Agnieszka Martowicz, Emil Lou, Wafik S. El-Deiry, Elisa Fontana, Pat Gulhati, Moh’d M. Khushman, Dominic Fong, Heinz-Josef Lenz, Dominik Wolf, Matthew James Oberley, Viktorija Sokolova; Department of Internal Medicine V (Hematology and Oncology), Comprehensive Cancer Center Innsbruck, Medical University of Innsbruck, Innsbruck, Austria; Department of Internal Medicine V (Hematology and Oncology), Medical University of Innsbruck, Comprehensive Cancer Center Innsbruck, Innsbruck, Austria; IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Medical Oncology and Hematology Unit, Milan, Italy; Caris Life Sciences, Irving, TX; Department of Pathology, Paracelsus University Salzburg, Salzburg, Austria; University of Minnesota, Minneapolis, MN; Brown University, Providence, RI; Sarah Cannon Research Institute UK, London, United Kingdom; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Washington University in St. Louis, Siteman Cancer Center, St. Louis, MO; Department of Hematology and Oncology, Hospital of Merano, Merano, Italy; Department of medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA; Caris Life Sciences, Phoenix, AZ; Hospital of Bolzano (SABES), Bolzano, Italy

Background: Encouraging pre-clinical efficacy targeting Exportin-1 (XPO1) - a master regulator of tumor suppressor protein export - has been reported in pancreatic ductal adenocarcinoma (PDAC) and clinical trials are currently ongoing. However, limited data is available regarding expression and function of XPO1 in PDAC. Thus, we investigated XPO1 mRNA expression and its clinical and immune correlates in PDAC. Methods: 5,488 PDACs were tested at Caris Life Sciences (Phoenix, AZ) with NGS of DNA (WES) and RNA (WTS). TMB-H was defined as $\geq 10 \text{mutations/MB}$. The cohort was stratified in quartiles according to XPO1 mRNA expression status, and XPO1-high (XPO1$^H$) and XPO1-low (XPO1$^L$) expression were defined as $\geq$top and $< \text{bottom quartile of transcripts per million (TPM)}$. Immune cell fraction was calculated by QuantiSeq method. Gene expression profiles were analyzed for transcriptomic signatures predictive of response to immune checkpoint inhibitors (T cell-inflamed score) and MAPK pathway activation (MPA). The Mann-Whitney U and X2 tests were applied as appropriate, with p-values adjusted for multiple comparisons. Real-world overall survival (OS) data was obtained from insurance claims. TCGA data were used to validate molecular, biological and immunological findings. Single-cell RNA analyses on a publicly available dataset were performed to elaborate cellular localization of XPO1. Results: Increased XPO1 mRNA expression was observed in metastatic lesions compared to primary tumors ($p<0.001$). Copy number amplification and mutation prevalence was comparable between XPO1$^H$ and XPO1$^L$ samples ($p>0.05$), along with similar rates of MSI-H/dMMR (1.3 vs 0.9%) and TMB-H (2.0 vs 1.3%; $p>0.05$). XPO1$^H$ PDACs were associated with a significant higher prevalence of T cell-inflamed tumors compared to XPO1$^L$ cases (58 vs 5%; $p<0.05$), consistent with higher immune cell infiltration in the XPO1$^H$ quartile as compared to XPO1$^L$ (p<0.05), except for immunosuppressive regulatory T cells and monocytes ($p>0.05$). XPO1$^H$ was associated with a higher MPA score as compared to XPO1$^L$ (2.4 vs -2.1 Arbitrary Units; $p<0.05$). XPO1$^H$ was associated with shorter OS (HR 1.09 [1.1-1.4], p=0.048). Validation studies using TCGA datasets corroborate our findings and confirmed increased immune cell infiltration as a function of XPO1. Moreover, single cell data revealed predominant and high expression of XPO1 in the tumor cell compartment. Conclusions: This is the first study comprehensively mapping XPO1 mRNA expression and immune-correlates in PDAC. We found that high XPO1 is linked to increased immune cell infiltration with a T cell-inflamed pattern. Our data provided a potential rationale to combine immune checkpoint therapy (+/- XPO1 inhibitors) in XPO1$^H$ PDACs. Research Sponsor: Southtyrolean Fund for the Promotion of scientific Research (SFPR) at the Southtyrolean Health Care System (SABES) and the Paracelsus Medical University Salzburg (PMU).
Clinical genomic implications of transcriptional subtypes in pancreatic cancer.

Harshabad Singh, Kevin S Kapner, Joanne Xiu, Matthew James Oberley, Alex Patrick Farrell, Jimmy Guo, Rishi Surana, Kimberly Perez, James M. Cleary, Srivatsan Raghavan, Benjamin Adam Weinberg, Michael J. Pishvaian, Rachna T. Shroff, Sanjay Goel, Stephanie Dougan, Jonathan Nowak, David Spetzler, George W. Sledge, Brian M. Wolpin, Andrew Aguirre; Dana-Farber Cancer Institute, Brookline, MA; Dana-Farber Cancer Institute, Cambridge, MA; Georgetown University Medical Center, Washington, DC; Johns Hopkins University School of Medicine, Washington, DC; University of Arizona Cancer Center, Tucson, AZ; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Brigham and Women’s Hospital, Boston, MA; Dana-Farber Cancer Institute Gastrointestinal Cancer Center, Boston, MA

Background: Transcriptional profiling of pancreatic cancers (PC) has defined classical and basal subtypes; basal tumors have worse outcomes. Mesenchymal (MES) and neural-like progenitor (NRP) subtypes are increasingly recognized and enriched post-therapy. Initial data suggests worse outcomes to FOLFIRINOX (FFX) compared with gemcitabine nab-Paclitaxel (GnP) in basal tumors. Several clinical trials are ongoing to investigate this. Here, we examined the clinical implications of transcriptional subtypes in a large, real-world dataset. Methods: Retrospective IRB exempt, deidentified data was examined from NextGen DNA and RNA sequencing performed on PCs at Caris Life Sciences (Phoenix, AZ). Classical and basal cell states were identified using RNA-seq and the PuriST algorithm in a genomic cohort or GATA6 and KRT5 expression levels in a clinical cohort. Tumor microenvironment immune cell composition on RNA seq was performed using QuantiSeq. Survival was obtained from insurance claims data and calculated from first treatment date to last known contact. Kaplan-Meier estimates were calculated for patient cohorts. P values were adjusted using Benjamini-Hochberg correction. Results: A total of 7,250 PCs were profiled in the genomic cohort. 3,063 tumors (42.2%) were strongly classical (SC), 2,015 tumors (27.8%) were strongly basal (SB) and the remaining had mixed phenotypes. MES and NRP marker genes were significantly co-expressed with each other, with basal genes, and anti-correlated with classical genes. When compared to SC, SB had significantly higher mutation rates in KRAS (93% vs. 88%), TP53 (83% vs. 72%) and ARID1A (12% vs. 8%), whereas SMAD4 (23% vs. 17%) mutations were more common in SC (all q < 0.05). There were no differences in mutation rates in homologous recombination or mismatch repair genes. SB had a significantly higher fraction of M1 macrophages (fold change [FC]: 1.14) and neutrophils (FC 1.16), whereas SC tumors had higher M2 macrophages (FC 1.18), NK (FC 1.2), and dendritic cells. Overall proportions of CD4/8 T cells were low and not different. Interestingly, SB had higher levels of PD-L1 by IHC (4.8% vs. 35%) and higher expression of immune exhaustion genes including CTLA4 (FC 1.19), TIM3 (FC 1.22) and PD-1 (FC 1.43) (all q < 0.05). The clinical cohort had 1,623 patients. Basal tumors had an inferior survival (median survival: 8.2 months (mo) vs 13.3 mo (Hazard Ratio (HR) 0.67, p < 0.00001)) and showed a significant improvement in outcomes when treated with upfront FFX vs GnP (n = 80 vs 90, Median: 15.8 vs 7.4 mos., HR 0.68, p = 0.021). This difference between FFX vs GnP was less pronounced in classical tumors (n = 70 vs 89, Median: 17.3 vs 15.4 mos, HR 0.70, p = 0.049). Conclusions: Our work represents the largest known real world molecular comparison of transcriptional subtypes of PC. Differential outcomes for patients with basal tumors treated with FFX versus GnP warrants further investigation in prospective studies. Research Sponsor: None.
Tumor mutational burden (TMB) in real-world patients with pancreatic ductal adenocarcinoma (PDAC): Differences in genomic alterations (GA) and predictive value for immune checkpoint inhibitor (ICI) effectiveness.

Amit Mahipal, Julia C. F. Quintanilha, Ryon Graf, Michael H. Storandt, Rachel B Keller, Gerald Li, Jeffrey S. Ross, Richard S.P. Huang, Alexa Betzig Schrock, Geoffrey R. Oxnard, Sakti Chakrabarti; UH Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Foundation Medicine, Inc., Boston, MA; Mayo Clinic, Rochester, MN; Foundation Medicine, Inc., Cambridge, MA; Foundation Medicine Inc, Morrisville, NC; University Hospital Seidman Cancer Center, Cleveland, OH

Background: Currently, ICI therapy is recommended for patients with metastatic PDAC whose tumors exhibit dMMR, MSI-H, or high TMB (≥10 mutations/Mb). However, due to the low prevalence of high TMB in PDAC (~1%), few studies have evaluated the role of ICI therapy in this subpopulation. This study aimed to compare GA between PDAC patients with high TMB and low TMB (< 10 mutations/Mb) and to evaluate the effectiveness of ICIs in real-world PDAC patients by TMB status. Methods: This study included PDAC patients who underwent genomic testing using Foundation Medicine tissue comprehensive genomic profiling (CGP) assays. GA were compared between tissue specimens with high and low TMB by chi-squared, adjusted for multiple comparisons. Patient clinical data was obtained by the US-wide de-identified Flatiron Health and Foundation Medicine real-world clinicogenomic pancreatic database (CGDB), originated from ~280 US cancer clinics between 01/2011 and 09/2022. Real-world overall survival (OS) and time to treatment discontinuation (TTD) were compared between patients receiving an ICI (high TMB versus low TMB) and between patients with high TMB (ICI versus other therapies) by Cox models. Results: We included 21,932 patients with PDAC with tissue CGP data available; 98.7% with low TMB and 1.3% with high TMB. Among actionable alterations, patients with high TMB had higher prevalence of mutations in BRCA2 (p < 0.0001), BRAF (p < 0.0001), PALB2 (p < 0.0001), and genes of the mismatch repair pathway (MSH2, MSH6, MLH1, and PMS2, p < 0.0001), but lower prevalence of KRAS mutations (p < 0.0001). The most common KRAS mutation in both groups of patients was G12D. In CGDB, 51 patients received an ICI (10 with high TMB and 41 with low TMB) and 17 patients with high TMB received other therapies. Among patients receiving an ICI, those with high TMB had more favorable median OS compared to those with low TMB (25.7 versus 5.2 months, hazard ratio (HR) 0.27, 95% confidence interval (CI) 0.09 - 0.76, p = 0.01) and median TTD (20.7 versus 3.0 months, HR 0.33, 95% CI 0.13 - 0.82, p = 0.02). Among patients with high TMB, those receiving an ICI had more favorable OS compared to those receiving other therapies (25.7 versus 6.6 months, HR 0.31, 95% CI 0.10-0.96, p = 0.043), nominally favoring ICI use in this small cohort (n = 10 versus 17). Conclusions: There is no randomized clinical trial evaluating ICI versus other therapies in PDAC. To our knowledge, this is the largest cohort to date comparing ICI effectiveness in PDAC. We observed more favorable OS among PDAC patients with high TMB receiving ICI versus those with low TMB who received an ICI and more favorable to those with high TMB receiving other therapies. This study supports the FDA-approved use of ICIs in patients with PDAC and high TMB and demonstrates the importance of TMB assessment for patients with PDAC. Research Sponsor: Foundation Medicine, Inc.
Randomized phase 2 study of nab-paclitaxel and gemcitabine with or without tocilizumab as first-line treatment in patients with advanced pancreatic cancer (PACTO).

Inna Markovna Chen, Julia S. Johansen, Susann Theile, Kasper Madsen, Olav Dajani, Torben Lorentzen, Teresa Zimmers, Dorte Nielsen; Copenhagen University Hospital - Herlev and Gentofte, Herlev, Herlev, Denmark; Oslo University Hospital, Oslo, Norway; Copenhagen University Hospital - Herlev and Gentofte, Herlev, Copenhagen, Denmark; Indiana University School of Medicine, Indianapolis, IN

Background: Pancreatic cancer (PC) presents one of the most aggressive malignancies for which currently available treatments are modestly effective. We report the findings of a randomized phase 2 trial (NCT02767557) to test the efficacy of gemcitabine/nab-paclitaxel (gem/nab) with or without tocilizumab (toc), as first-line treatment in patients with locally advanced or metastatic PC.

Methods: Prior to randomization, a safety cohort of 6 participants received gem 1000 mg/m2, nab 125 mg/m2 (days 1, 8, and 15 of each 28-day cycle) and toc 8 mg/kg (day 1 of each cycle). Participants were then randomized 1:1 to receive gem/nab or gem/nab/toc. Patients had modified Glasgow Prognostic Score of 1 or 2 and were stratified by performance status (PS) and stage. The primary endpoint was the overall survival (OS) rate at 6 months (OS6). Secondary end points included median progression-free survival (PFS), median OS, overall response rate (ORR), and safety.

Results: A total of 147 patients were treated; 141 were randomized to receive gem/nab/toc (n = 70), or gem/nab (n = 71). As of January 9, 2023, the median follow-up was 8.1 months (IQR 4.2–13.9). OS6 was 68.6% (95% CI, 56.3-78.1) in gem/nab/toc group and 62.0% (95% CI, 49.6-72.1) in gem/nab group (p = 0.41). No significant differences in the median OS or PFS were observed between the gem/nab/toc group and the gem/nab group (OS, 8.4 versus 8.0 months; HR, 0.75; 95% CI, 0.54-1.05; p = 0.10), and (PFS, 5.6 versus 5.5 months; HR, 0.85; 95% CI, 0.61-1.20; p = 0.36). The 12, 18 and 24-month OS rates were 37.1% (95% CI, 26.0-48.3%), 27.1% (17.4%-37.8%), 10% (4.4%-18.3%) for gem/nab/toc and 28.2% (18.3%-38.9%), 7.0% (2.6%-14.5%), 2.8% (0.5%-8.8%) for gem/nab, respectively. The ORR was 37.1% (95% CI, 25.9%-49.5%) in gem/nab/toc group and 35.2% (24.2%-47.5%) in gem/nab group. The incidence of grade 3 or higher treatment related adverse events was 88.2% in gem/nab/toc and 63.4% in gem/nab group (p < 0.001). Of those, neutropenia (55.3% versus 16.9%), and thrombocytopenia (40.8% versus 11.3%) were most common. Two and one treatment-related deaths, respectively, in gem/nab/toc and gem/nab group, occurred during the study.

Conclusions: In patients with advanced PC, the addition of tocilizumab to gem/nab did not result in improved OS rate at 6 months. Although more patients were alive at 18 months in the gem/nab/toc, long-term survival rates exceeding 24 months were not different between groups. The biomarkers for selection of patients who might benefit from gem/nab combined with tocilizumab are to be identified. Clinical trial information: NCT02767557. Research Sponsor: Celgene; Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark.
Efficacy of immune checkpoint inhibitors in microsatellite unstable/mismatch repair-deficient advanced pancreatic adenocarcinoma: An AGEO European Cohort.

Lorenzo Pilla, Lina Sayah, Kathrin Heinrich, Volker Kunzmann, Alice Boileve, Geert A. Cirkel, Sara Lonardi, Benoist Chibaudel, Anthony Turpin, Tamar Beller, Vincent Hautefeuille, Caterina Vivaldi, Thibault Mazard, Lucile Bauguion, Monica Niger, Gerald W. Prager, Clélie Coutzaz, Benedikt Westphalen, Edouard Auclin, Julien Taieb; Department of Gastroenterology and Gastrointestinal Oncology, Hôpital Européen Georges-Pompidou, AP-HP, Université de Paris, Paris, France; Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany; University of Wuerzburg/Medizinische Klinik 2, Würzburg, Germany; Digestive Department, Gustave Roussy Institut, Villejuif, France; Department of Medical Oncology, University Medical Center Utrecht, Utrecht, Netherlands; Department of Oncology, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Department of Medical Oncology, Franco-British Hospital, Fondation Cognacq-Jay, Levallois-Perret, France; Medical Oncology Department, Lille University Hospital, University of Lille, Lille, France; Oncology Institute, Sheba Medical Center, Ramat Gan, Israel; Department of Gastroenterology, Amiens University Hospital, Amiens, France; Azienda Ospedaliero-Universitaria Pisana - Department of Translational Research and New Technologies in Medicine, University of Pisa, Pisa, Italy; IRCM, Institut de Recherche en Cancérologie de Montpellier, INSERM U1194, Université de Montpellier, Institut Régional du Cancer de Montpellier, Montpellier, France; Hepatogastroenterology Department, Centre Hospitalier Départemental Vendée, La Roche-Sur-Yon, France; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Medical University of Vienna, Vienna, Austria; Centre Léon Bérard, Lyon, France; Comprehensive Cancer Center Munich and Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; Oncology Department, Hôpital Européen Georges Pompidou, AP-HP, University of Paris, Paris, France; Georges Pompidou European Hospital, SIRIC-CARPEM, Université de Paris, Paris, France

Background: Immune checkpoint inhibitors (ICI) have been approved for the use in solid tumors with MSI/dMMR. Nevertheless, the outcome of patients (pts) with MSI/dMMR pancreatic ductal adenocarcinoma (PDAC) seems poorer when compared to other malignancies. This multi-institutional analysis aimed to assess the efficacy and tolerability of ICIs in a large real-world cohort of pts with MSI/dMMR PDAC. Methods: Retrospective data were collected for pts with MSI/dMMR PDAC treated with ICIs from February 2016 to May 2022 in 16 different centers across Europe and Israel. Progression-free survival (PFS) and overall survival (OS) were calculated from the start of treatment, and objective response (OR) and disease control rate (DCR) were measured according to RECIST V1.1. Results: We identified 31 pts with metastatic MSI/dMMR PDAC. The mean age was 62.1 years (range: 37-82), 45.1% were female and ECOG PS status was predominantly 0 or 1 (83.9%). At the time of ICI treatment 1 pt had locally advanced and 30 had metastatic disease. MSH2/MSH6 deficiency (def) was found in 9 cases, MLH1/PMS2 def in 7, MSH 6 def in 4, MSH 2 def in 3, PMS2 def in 3 and MLH1/MSH6/PMS2 def and a CpG highland methylator phenotype in 1 pt. MMR status was not available in 4 pts. Germline mutation testing was performed in 20/31 pts (64.5%) and Lynch syndrome was diagnosed in 8 pts (45%). Nineteen pts received pembrolizumab, 8 received nivolumab, 1 received lopotolimab and 3 received ipilimumab/nivolumab (ipi/nivo). The mean number of prior lines of chemotherapy was 1.5 (range 0-4). Among the 31 pts in this analysis, 15 (48.4%) had an OR (3: complete response and 12 partial response) and 6 (19.3%) had stable disease, resulting in a DCR of 67.7%. Ten pts had disease progression (PD) (32.3%). Median PFS was 26.7 months and median OS was not reached with median follow-up (FU) of 18 months. Median duration of response was not reached (95%CI:24.1-NR). Analysis of all responders, with a follow up of 12 months or more (n:14), showed that 100% of them maintained their response. In addition 71% of the pts of this cohort are still alive with a median time of follow up since the diagnosis of metastatic disease of 39.9 months. After ICIs discontinuation, 6 pts received chemotherapy. One pt who had PD after 15 months of pembrolizumab switched to ipi/nivo and achieved a CR. Immunotherapy was generally well tolerated; No Grade 3-5 adverse events (AEs) were reported and no therapy discontinuation due an adverse event was observed. Conclusions: This retrospective analysis suggests that ICIs are effective and well tolerated in pts with MSI/dMMR advanced PDAC. Hence, our work supports the use of PD-1 inhibition in this group of pts with high unmet medical need. Research Sponsor: None.
Validation of the PDACai signature in predicting relative benefit from frontline FOLFIRINOX (FFX) and gemcitabine/nab-paclitaxel (GA) for patients (pts) with metastatic pancreatic cancer (mPDAC).

Michael J. Pishvaian, Edik Matthew Blais, Dzung Thach, Jonathan Robert Brody, Lynn McCormick Matrisian, David Charles Halverson, Patricia DeArbeloa, Flavio G Rocha, Andrew Eugene Hendifar, Emanuel Petricoin; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Washington, DC; Perthera, South San Francisco, CA; Perthera, Mclean, VA; Oregon Health & Science University, Portland, OR; Pancreatic Cancer Action Network, Manhattan Beach, CA; Perthera, Holliston, MA; Cedars-Sinai Medical Center, Los Angeles, CA; George Mason University, Manassas, VA

Background: Nearly 50% of pts with mPDAC never receive a 2nd line of therapy for metastatic disease following frontline FFX or GA. Genomic alterations in the DDR pathway (e.g. BRCA1/2) are associated with increased progression-free survival (PFS) on platinum-containing regimens (e.g. FFX), but other biomarker-treatment associations that predict benefit from GA and/or FFX in mPDAC remain unexplored. In this retrospective real-world evidence (RWE) study, we use a data-driven machine learning approach to gain new insights from the mutational landscape in mPDAC and validate the PDACai signature in predicting personalized benefit from both FFX and GA. Methods: We analyzed real-world outcomes from 711 pts with mPDAC who underwent genomic profiling via the Know Your Tumor program or were referred to Perthera by treating oncologists. Chart-abstracted PFS data on either 1st line FFX or GA were split (60:40) into independent training and validation cohorts for each regimen. All models integrate a shared set of clinical (age < 63, sex) and lab-agnostic molecular features derived from clinical NGS testing reports (DDR pathway alterations, specific KRAS variants, frequently mutated genes). Relative benefit scores predicted by FFX or GA models were evenly binned into three PDACai signature categories representing lower, middle, and upper tertiles for each independent cohort. Statistical differences in median PFS were evaluated using ordinal Cox regression. Results: Median PFS followed predicted trends as generated by PDACai for each therapy in training and validation cohorts. The predictive utility of PDACai was confirmed in the independent validation cohorts when comparing PFS on FFX (p = 0.03744; HR = 0.75 [95% CI: 0.58-0.98]) and GA (p = 0.00006861; HR = 0.65 [95% CI: 0.53-0.8]) across tertiles. Conclusions: Response to chemotherapy is heterogeneous and difficult to predict in pts with mPDAC. Using RWE, the PDACai signature successfully predicted relative differences in PFS on both FFX and GA in mPDAC. With prospective validation, personalized insights generated by PDACai from pts with similar biomarker profiles could be used to tailor treatment sequencing in pts with NGS testing results, particularly those without actionable genomic findings. Research Sponsor: Pancreatic Cancer Action Network; Perthera.

<table>
<thead>
<tr>
<th>Independent Cohort (# Pts)</th>
<th>Lower Tertile mPFS (95% CI)</th>
<th>Middle Tertile mPFS (95% CI)</th>
<th>Upper Tertile mPFS (95% CI)</th>
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<tr>
<td>1st line FFX Training (212)</td>
<td>6.4 [5.6-7.5]</td>
<td>8.0 [6.1-10.6]</td>
<td>15.8 [10.3-N/R]</td>
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<tr>
<td>1st line GA Training (209)</td>
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<td>7.3 [5.8-8.4]</td>
<td>10.1 [8.1-12.1]</td>
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<tr>
<td>1st line GA Validation (145)</td>
<td>5.6 [4.7-8.6]</td>
<td>8.2 [6.5-15.6]</td>
<td>8.8 [7.7-13.9]</td>
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Background: Frontline treatment for advanced pancreatic ductal adenocarcinoma (PDAC) has been either 5-fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX) or gemcitabine and nab-paclitaxel (GP) for the past decade. While the NAPOLI-3 trial, utilizing liposomal irinotecan, highlighted the superiority of a triplet regimen over GP, the question remains whether certain subgroups may derive particular benefit from GP. Pre-clinical data in lung cancer suggest that KRAS G12C may facilitate enhanced DNA adduct removal after platinum chemotherapy and confer resistance to this drug class. While multiple KRAS G12C inhibitors have shown early promise in PDAC, multi-agent chemotherapy remains the frontline standard and will likely remain an important therapeutic tool. This study aimed to investigate clinical outcomes after platinum and non-platinum-based chemotherapy in patients with advanced KRAS G12C-mutated PDAC.

Methods: PDAC samples were tested using whole transcriptome sequencing (WTS; Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) at Caris Life Sciences (Phoenix, AZ). Significance was determined by X² and Fisher-Exact and p adjusted for multiple comparisons (q). Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from first of treatment to last contact with comparison done by Kaplan-Meier test.

Results: A total of 5,555 PDAC patients harboring KRAS pathogenic variants were identified, including 109 with a G12C mutation. For KRAS G12C mutants, median overall survival was 470 days for those who received GP (n=22) compared to 240 days for patients who received FOLFIRINOX (n=9) with a median difference of 230 days (HR 0.32, CI 0.12-0.82, p=0.013). In contrast, median overall survival was higher for patients harboring G12D (392 vs 297 days, p=0.003), G12V (500 vs 356 days, p=0.012) or G12R (469 vs 391 days, p=0.095) mutations who received FOLFIRINOX compared to GP. KRAS G12C mutated PDAC showed the highest rate of PDL1+ staining (27%) compared to other variants (G12R 13% and G12D 19%, q,0.01). TMB-H and MSI-H prevalence were highest in G12C compared to other variants (no statistical significance observed).

Conclusions: In patients with advanced PDAC and a G12C mutation, median overall survival appears significantly longer in those treated with GP compared to FOLFIRINOX. The opposite trend was seen in patients with other KRAS variants including G12D, G12V, and G12R, consistent with the recently presented NAPOLI-3 trial. PDL1 staining was also highest in the KRAS G12C cohort. While this is the largest reported analysis of outcomes to frontline chemotherapy in KRAS G12C-mutated PDAC, the sample size is small and needs validation in additional datasets. Next steps include evaluating DNA mutational status and RNA expression of genes involved in DNA repair in G12C vs other KRAS variants to better understand the outcome data presented here. Research Sponsor: None.
Background: Individuals with Down syndrome (DS) have a lower risk for solid tumors and angiogenesis related diseases. DSCR1 is highly upregulated in DS patients and its product, calcipressin-1, was shown to suppress angiogenesis and reduce cancer risk. High DSCR1 expression has been reported to decrease PDAC growth and metastasis in animal models. Here, we analyzed the molecular features and clinical outcomes associated with DSCR1 expression in PDAC.

Methods: 8352 tumor samples tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) were analyzed. Top quartile transcripts per million for DSCR1 expression were considered high (Q4) while bottom quartile low (Q1). Cell infiltration in the tumor microenvironment (TME) was estimated using QuantiSEQ. Interferon-gamma (IFG) and T-cell expression were considered high (Q4) while bottom quartile low (Q1). DSCR1 expression in PDAC in immune-related biomarkers (TMB, dMMR/MSI-H and PD-L1 protein), gene mutations which were more frequent in DSCR1 Q4 (93 vs 86%, Q4 vs Q1, q < .0001). Gene set enrichment analysis showed that DSCR1 high tumors were enriched in alterations of several pathways including NOTCH signaling, DNA repair, IFG response, myogenesis and adipogenesis (P < .05, false discovery rate < .25). B cells, M1 and M2 macrophages, neutrophils, NK cells, and Tregs were more abundant in the TME of tumors with high DSCR1 while dendritic cells, CD4+ T cells and monocytes were lower (q < .05). DSCR1 Q4 was associated with higher TIS score (50% inflamed vs 3.6%, q < .05) and positively associated with immune-related gene expression including CTLA4, IDO1, CD80, PD-L1, LAG3, CD86, TIM3, IFG, PD-1, and PD-L2 (fold change: 2.4, q < .0001). Overall, DSCR1 expression above median was associated with longer median OS (17 vs 11 months, HR 0.89 [0.83-0.95], P < .0001). When stratified by quartiles, DSCR1 Q4 was associated with longer time on treatment (ToT) with gemcitabine/nab-paclitaxel (HR 0.75 [0.63-0.89], P = .001), and marginal benefit on ToT (HR 0.81 [0.65-1.0]) but longer survival in FOLFIRINOX treated patients (HR 0.73 [0.58-0.92], P = .008).

Conclusions: This is the first and most extensive profiling study to investigate DSCR1 expression in PDAC. Our data show a strong association between tumor DSCR1 gene expression, several pathway alterations, immune-related gene expression, TME cell infiltration and patient survival. These findings suggest DSCR1 as a candidate prognostic biomarker and as a potential treatment target in PDAC.

Research Sponsor: This work was partly supported by National Cancer Institute (P30CA014089), Gene Gregg Pancreas Research Fund, Ming Hsieh research fund, Dhont Family Foundation, San Pedro Peninsula Cancer Guild; Daniel Butler Research Fund, V foundation for cancer research, Victoria and Philip Wilson Research Fund, Fong research project and Gloria Borges WunderGlo Foundation.

Tara Mackay, Anouk EJ Latenstein, Simone Augustinus, Lydia G. van der Geest, Auke Bogte, Bert A. Bonsing, Hendrik Bos, Koop Bosscha, Lodewijk Brosens, Geert A. Cirkel, Lieve Hol, Olivier R.C. Busch, Geert-Jan Creemers, Wouter L. Curvers, Sarah Derks, Jeanin E. van Hooft, Casper H.J. Van Eijck, Johanna Wilmink, Hanneke W.M. Van Laarhoven, Marc G. Besselink, for the Dutch Pancreatic Cancer Group; Amsterdam UMC, Location University of Amsterdam, Department of Surgery, Amsterdam, Netherlands; Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, Netherlands; Department of Gastroenterology and Hepatology, University Medical Center Utrecht, the Netherlands, Utrecht, Netherlands; Leiden University Medical Center, Leiden, Netherlands; Department of Medial Oncology, Tjongerschans Hospital, Heerenveen, Netherlands; Department of Surgery, Jeroen Bosch Hospital, Den Bosch, Netherlands; Department of Pathology, University Medical Center Utrecht, Utrecht, Netherlands; Department of Medical Oncology, Regional Academic Cancer Center Utrecht, University Medical Center Utrecht & St. Antonius Hospital Nieuwegein, Utrecht, Netherlands; Department of Gastroenterology, Catharina Hospital, Eindhoven, Netherlands; Department of Gastroenterology, Catharina Hospital, Eindhoven, Netherlands; Amsterdam UMC, location University of Amsterdam, Department of Medical Oncology, Amsterdam, Netherlands; Department of Surgery, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands; Department of Medical Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

Background: Implementation of new treatment strategies in cancer care is often inadequate and slow. We aimed to implement best practices in pancreatic cancer care using a nationwide stepped wedge design and assess the impact on overall survival. Methods: Nationwide multicenter stepped-wedge cluster randomized controlled trial comparing implementation of best practices with usual care (May 22, 2018 – May 29, 2020). Best practices included adequate use of perioperative and palliative chemotherapy, pancreatic enzyme replacement therapy (PERT), and metal biliary stents. The 6-week implementation period in all 17 Dutch pancreatic centers and their regional referral networks included monitoring, return visits, and provider feedback in combination with education and reminders. Primary outcome was one-year overall survival for all disease stages and secondary outcomes included guideline compliance and quality of life. Results: Overall, 5580 patients diagnosed with pancreatic cancer were included; 2939 after implementation of best practices versus 2641 before. One-year survival did not differ among the groups (HR 0.98, 95 CI 0.88-1.08). Overall use of perioperative chemotherapy (neoadjuvant and adjuvant) did not significantly differ, but use of palliative chemotherapy significantly increased (23.9% to 30.3%, OR 1.38, 95 CI 1.10-1.74). Also the use of PERT (34.2% to 45.2%, OR 1.64, 95 CI 1.28-2.11); and metal biliary stents (74.1.% to 83.3%, OR 1.78, 95 CI 1.13-2.08) significantly increased. The Global Health Score did not differ (AUC 43.8 to 42.7, median difference -1.12, 95 CI -3.13-0.80, n=655). Conclusions: This nationwide population-based trial to enhance implementation of best practices in pancreatic cancer care showed successful implementation of most best practices, but no increase in one-year survival and quality of life. Clinical trial information: NCT03513705. Research Sponsor: This research was funded by a grant from the Dutch Cancer Society (grant number UVA2013-5842).
First in class TLR7/8 agonist BDB001 combined with atezolizumab and stereotactic body radiation therapy in patients with advanced pancreatic adenocarcinoma: Results from the AGADIR study.

Simon Pernot, Paul Sargos, Philippe Rochigneux, François Ghiringhelli, Lola Jade Palmieri, Sophie Cousin, Jean Philippe Guégan, Jean David Fumet, Vincent Bourbonne, Alban Bessede, Jean Philippe Metges, Antoine Italiano; Department of Medical Oncology, Institute Bergonié Cancer Center, Bordeaux, France; Department of Radiation Oncology, Institut Bergonie, Bordeaux, France; Institut Paoli-Calmettes, Marseille, France; Early clinical unit CLIP2 INCA, Centre GF LECLERC, Dijon, France; Medical oncology Department, Institut Bergonie, Bordeaux, France; Medical Oncology Department, Institut Bergonie, Bordeaux, France; Georges François Leclerc Cancer Center – UNICANCER, Dijon, France; Medical oncology Department, CHU Brest, Brest, France; EXPLICYTE, Bordeaux, France; CHU De Brest, Landerneau, France; Early Phase Trials Unit, Institut Bergonié, Bordeaux, France

Background: Pancreatic adenocarcinoma is refractory to immune checkpoint inhibitors such as PD1/PDL1 antagonists. Investigating alternative immunotherapeutic approaches is a crucial need for this devastating disease. The potent immunostimulatory effects of Toll-like receptor (TLRs) have spurred efforts aimed at the development of TLR agonists as new immune-oncology agents. Radiation therapy combined with TLRs agonists has been shown to enhance antitumor immunity in the preclinical setting.

Methods: AGADIR is a multi-cohort, phase 2, multicenter, open-label study investigating the novel TLR 7/8 agonist BDB001 combined with atezolizumab and stereotactic body radiotherapy (SBRT) in patients with advanced cancers. Cohort A enrolled patients with advanced pancreatic adenocarcinoma. BDB001 was administered IV at the dose of 0.75 mg/m² on days 1, 8, and 15 of cycles 1, 2, and 3. Then from cycle 4 on day 1 every 3 weeks. Atezolizumab was given at the dose of 1200 mg every 3 weeks. SBRT of at least one metastatic lesion was started at least one week after the first administration of atezolizumab and at the latest before the Cycle 2 Day 1. The primary endpoint is disease control rate defined as the proportion of participants with complete response, partial response or stable disease, as per adapted RECIST v1.1, observed within 24 weeks of treatment onset. Secondary endpoints include objective response, progression-free survival, overall survival and safety. All patients underwent sequential blood and tissue sampling for translational studies.

Results: Between July 2021, and June 2022, 32 pts were enrolled in 3 centers (14 male, 18 female). Median age was 64 years (range 38 – 78). Median number of previous treatment lines was 1 (range 1 – 5). The most common treatment related adverse events were grade 1/2 asthenia, chills and fever. No death was related to the treatment. Among the 21 patients for whom central review was performed at the time of this writing, best tumor response was confirmed partial response, stable disease and progressive disease in 2 (9.5%), 6 (28.5%) and 13 (62.0%) patients respectively. The disease control rate was 38.0% (95%CI 18.1-61.5).

Conclusions: The AGADIR study met its first endpoint for disease control rate in patients with advanced pancreatic cancer. Efficacy data on the whole cohort of patients and full biomarkers analyses will be presented at the meeting. Clinical trial information: NCT03915678. Research Sponsor: Institut National du Cancer; Roche Parma AG, Seven and Eight Biopharmaceuticals Inc.
Clinical utility of next generation sequencing (NGS) on circulating tumor DNA (ctDNA) in patients (pts) with pancreatic cancer (PC).

Fergus Keane, Lily Saadat, Catherine O’Connor, Joanne F. Chou, Angela Rose Brannon, Darren Cowzer, Fionnuala Crowley, Neha Debnath, Anita Bowman, Fei Xu, Wungki Park, Alice Zervoudakis, Fiyinfolu Balogun, Anna M. Varghese, Kenneth H. Yu, David Paul Kelsen, Marinela Capanu, Michael F. Berger, Alice Chia-chi Wei, Eileen Mary O’Reilly; Memorial Sloan Kettering Cancer Center, New York, NY; Brigham and Women’s Hospital, Boston, MA; Department of Epidemiology & Biostatistics, Memorial Sloan Kettering, New York, NY; Mount Sinai Morningside West, New York, NY; Icahn School of Medicine at Mount Sinai Morningside/West, New York, NY

Background: ctDNA provides opportunities for identifying targeted therapies, a source to conduct NGS when tissue acquisition is infeasible, detection of minimal residual disease (MRD), and identification of resistance mutations. There are limited large data sets to inform clinical utility and limited correlation of NGS of ctDNA and tumor in PC. Herein, we evaluate the ctDNA detection rate in multiple cohorts of PC and report the ctDNA-tissue genotype concordance in PC at Memorial Sloan Kettering (MSK). Methods: Pts with PC at MSK who had ctDNA prospectively collected using the MSK-ACCESS 129 gene ctDNA NGS assay, were identified. ctDNA detection was defined as the identification of a mutation, copy number (no.) alteration or structural variant. Tissue-based NGS using MSK-IMPACT gene assay was performed for pts with adequate tissue, and matched with ctDNA by date. Clinical, pathologic and outcome data were abstracted. Data are summarized with descriptive statistics. Overall survival (OS) estimated by Kaplan-Meier method from date of ctDNA draw to death/last follow up. Results: From 08/2019 to 07/2022, N= 414 pts with PC and ≥ 1 ctDNA sample included. Median age 69 years (range 29-92), female N=206 (50%). Stage at ctDNA collection: Stage I-III N= 203 (49%); Stage IV N= 211 (51%). ctDNA detection rate by no. of involved organs: 0 organs (MRD), N=7/30 (23%); 1-2 organs, N=158/270 (58.5%); 3-4 organs, N=82/102 (80.4%); >5 organs, 12/12 (100%). ctDNA detection rate by site of metastasis; Liver only, 75/99 (76%); peritoneum only, 15/25 (60%); lung only, 10/22 (45%). In pts with detected ctDNA median CA 19-9 was 494 U/mL (range 0, 247674) vs 100 U/mL (range 1, 22360) in pts with undetected ctDNA. In pts with detected ctDNA median CEA was 7 ng/mL (range 1, 2020) vs 4 ng/mL (range 1, 99) in pts with undetected ctDNA. In stage IV untreated pts, median OS 13 months(m) (95% CI; 7.3, 16) and 10 m (95% CI; 5.6, 15) for ctDNA detected vs undetected, respectively. ctDNA detection rates by stage, and concordance between ctDNA and tissue-based NGS for common driver mutations KRAS, TP53, CDKN2A and SMAD4 in N=131 matched pairs are summarized in the table. Conclusions: ctDNA detection rates are high (89%) in pts with untreated stage IV PC, with high concordance between ctDNA and tissue-based NGS for common driver mutations KRAS, TP53, CDKN2A and SMAD4 in N=131 matched pairs are summarized in the table. ctDNA is a promising tool in detection of somatic alterations in PC, particularly in stage IV disease, and is a complementary adjunct to tumor-based NGS. Research Sponsor: None.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>ctDNA Detected N (%)</th>
<th>ctDNA Undetected N (%)</th>
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<tr>
<td>Stage IV Untreated</td>
<td>119</td>
<td>106 (89%)</td>
<td>13 (11%)</td>
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<tr>
<td>Stage I–III Untreated</td>
<td>61</td>
<td>26 (43%)</td>
<td>35 (57%)</td>
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<tr>
<td>MRD</td>
<td>30</td>
<td>7 (23%)</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Concordance Per Gene</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>76%</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>TP53</td>
<td>76%</td>
<td>89%</td>
<td>50%</td>
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<tr>
<td>CDKN2A</td>
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</tr>
<tr>
<td>SMAD4</td>
<td>85%</td>
<td>87%</td>
<td>89%</td>
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</table>
Impact of novel pan-RAS inhibitors on efficacy and resistance to AMG-510 and MRTX-1133 in pancreatic cancer cell lines.

Tariq Arshad, Howard Donninger, Becca von Baby, Rachel Ferrill, Joe Burlison, John Trent, Geoffrey J. Clark; Qualigen Therapeutics, San Ramon, CA; Dept. Medicine, Brown Cancer Center University of Louisville, Louisville, KY; Departments of Medicine and Pharmacology & Toxicology, James Graham Brown Cancer Center, University of Louisville, Louisville, KY; Dept. Pharm/Tox, Brown Cancer Center University of Louisville, Louisville, KY

Background: Mutant-activated RAS genes are the most frequently mutated gene family associated with cancer (almost 30% of all cancers contain a mutant RAS gene). KRAS is the predominant isoform mutated in cancer and is the isoform exclusively mutated in pancreatic ductal carcinoma (PDAC). Since almost all PDAC cases harbor a mutant RAS, it is arguably the most RAS-addicted tumor type. There is now considerable evidence implicating mutant KRAS as a driver of PDAC. Recently, several mutant KRAS-targeted therapies (sotorasib and adagrasib) have been developed and show promise in PDAC patients. We have developed a direct inhibitor of RAS with a predicted unique interaction region capable of directly binding to wild-type H- and K-RAS, but which shows preferential binding for KRAS G12D and G12C mutants. This novel inhibitor disrupts the RAS effector domain and blocks the ability of RAS to signal through its effectors. Methods: We used in silico virtual library screening to identify an initial candidate inhibitor which was effective at inhibiting the 3D growth of PDAC cells without affecting their growth in 2D. Subsequent iterative rounds of medicinal chemistry was then performed to identify a series of derivatives with enhanced activity, as determined by 3D growth inhibition assays and effects on Ras signaling, as determined by Western blot analysis of phosphor-ERK, phosphor-Akt and activation of Ral A. Results: Our series of RAS inhibitors effectively block PDAC cell growth in 3D without impacting their 2D proliferation and suppress the interaction of KRAS with its effector cRAF. The inhibitors also effectively inhibit RAS signaling in mutant RAS containing PDAC cells. Since our novel compounds are predicted to bind to RAS at a different site to either AMG-510 (G12C specific inhibitor) and MRTX-1133 (G12D specific inhibitor), we tested the co-operativity of our compounds with these existing agents. Our compounds enhanced the anti-proliferative effects of both MRTX-113 and AMG-510 in mutant KRAS G12D and G12C PDAC cells, respectively. Conclusions: We have developed a series of novel RAS inhibitors that directly bind preferentially to mutant KRAS that may serve as new mutant KRAS-targeted therapeutics, and that may also have the potential to enhance the efficacy or suppress the resistance of AMG-510 and MRTX-1133. Research Sponsor: Qualigen Therapeutics; U.S. National Institutes of Health.
Targeting germline or somatic DNA repair defects (beyond BRCA) in pancreatic cancer with niraparib: A phase II study (NIRA-PANC).

Anup Kasi, Junqiang Dai, Raed Moh’d Taiseer Al-Rajabi, Joaquina Celebre Baranda, Anwaar Saeed, Prabhakar Chalise, Erin Carroll, Shannon Bradbury, Stephen Hyter, Malgorzata Anna Witek, Venkatadri Beeki, Richard J. McKittrick, Manidhar Reddy Lekkala, Anusha Chidharla, Sean Kumer, Timothy Schmitt, Stephen K. Williamson, Steven Soper, Andrew K. Godwin, Weijing Sun; University of Kansas Cancer Center, Westwood, KS; The University of Kansas Medical Center, Kansas City, KS; University of Kansas Medical Center, Kansas, KS; University of Kansas Medical Center, Kansas City, KS; University of Kansas Cancer Center UKH - Southwest Office, Topeka, KS; University of Kansas Cancer Center, Kansas City, KS

Background: Targeting a molecular subset of pancreatic cancer (PC) may identify alternatives to perpetual chemotherapy and chemo-resistance/toxicity. Poly (ADP ribose) polymerase inhibitors (PARPi) have shown efficacy in germline BRCA mutation via synthetic lethality. Preclinical evidence suggests PARPi may target DNA repair defects beyond BRCA. We conducted a Niraparib phase II study in PC patients with germline/somatic DNA repair defects. Methods: This is an open-label, phase 2 trial in pts with locally advanced or metastatic PC with germline or somatic mutations, known or tested after consent to pre-screening tumor tissue analysis in DNA repair genes (BRCA1/2, PALB2, ATM, NBN, ATR, BRIP1, IDH1/2, RAD51, RAD51B/C/D, RAD54L, CDK12, BARD1, FAM175A, BAP1, CHEK1/2, GEN1, MRE11A, XRCC2, SHFM1, FANC2, FANCA, FANCC, FANC, RPA1, ARID1A), who have progressed on or intolerant of at least one line of therapy, no prior PARPi, with evaluable disease, and ECOG PS 0-1. Eligible pts were treated with Niraparib 300mg or 200mg PO daily for 28 days (1 cycle = 28 days) (200mg dose for baseline weight is < 77 kg or baseline platelet count is < 150,000 μL) until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent, or death. The primary objective was 6-month PFS rate. The secondary objectives were OS, DCR and safety. Pts were evaluable for safety if they had received ≥ 1 dose of Niraparib and for efficacy if they had also received ≥ 1 follow-up imaging study. Results: As of Feb 2023, 36 (13 female, 23 male) pts were enrolled, with a mean age of 62.9 (median 64, IQR 51-73, min 41, max 83, SD 11.25), of whom 27 (8 female, 19 male) were evaluable for efficacy. After a median follow-up of 9.0 months (IQR 6.0-15.1 m), the 6-month PFS rate was 40.7% (11/27 pts; 95% CI 4.7%- 100 %). The median PFS is 4.4 m (CI 2.3 - 6.5 m), and median OS is 9.1 m (7.5 -15.1 m). The disease control rate at 8 weeks was 70.4% (19 of 27 pts; 95% CI 49.8%-86.3%). Of the 27 evaluable pts- BRCA2 mutation was seen in 10 pts, ATM (5), CHEK2 (5), BRCA1 (2), NBN (2), ARID1A (1), FANCA (1), FAM175 A (1), RAD51B (1), IDH1 (1), IDH2 (1). Among 36 pts evaluable for safety, treatment-related adverse events occurred in 75% (27/36), and Grade 3 and grade 4 treatment-related adverse events occurred in 19% (7/36), and Grade 3 and grade 4 treatment-related adverse events occurred in 31% (11/36). The most common treatment-related AEs were anemia (25%, 9/36), nausea (22%, 8/36), thrombocytopenia (19%, 7/36), vomiting (19%, 7/36), and fatigue (17%, 6/36). Serious treatment-emergent adverse events were reported in 11% (4/36). There were no treatment-related deaths. Conclusions: In previously treated pts with locally advanced and metastatic PC harboring DNA repair defects, niraparib monotherapy yielded a 6-month PFS rate of 40%, median PFS of 4.4 months, and median OS of 9.1 months. Clinical trial information: NCT03553004. Research Sponsor: GSK (TESARO); IIT Steering Committee funds at KU Cancer Center.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pts (n =27)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6m-PFS</td>
<td>40.7% (11/27)</td>
<td>4.7%-100%</td>
</tr>
<tr>
<td>mPFS</td>
<td>4.4 months</td>
<td>2.3 - 6.5 m</td>
</tr>
<tr>
<td>mOS</td>
<td>9.1 months</td>
<td>7.5 -15.1 m</td>
</tr>
<tr>
<td>DCR</td>
<td>70.4% (19/27)</td>
<td>49.8%-86.3%</td>
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Chemotherapy dose density and effect on prognosis for patients with resectable pancreas cancer: A secondary analysis of SWOG S1505.

Sameer H. Patel, Sarah Colby, Davendra Sohal, Katherine A Guthrie, Lisa A. Kachnic, E. Gabriela Chiorean, Andrew M. Lowy, Flavio G Rocha, Philip Agop Philip, Syed Ahmad; University of Cincinnati Medical Center, Cincinnati, OH; SWOG Statistical Center, Seattle, WA; University of Cincinnati, Cincinnati, OH; Fred Hutchinson Cancer Research Center, and SWOG Statistics and Data Management Center, Seattle, WA; New York Presbyterian - Columbia, New York, NY; University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; Department of Medical Oncology, University of California, San Diego, CA; Oregon Health & Science University, Portland, OR; Hoag Family Cancer Institute, Newport Beach, CA; Cincinnati College of Medicine, Cincinnati, OH

Background: Chemotherapy is an integral part of multimodality treatment for resectable pancreatic ductal adenocarcinoma (PDAC). Assessing the impact of chemotherapy dose reductions or missed cycles on survival is difficult as few trials prospectively address the prognostic value of this important metric. Methods: SWOG S1505 (NCT02562716) was a randomized, phase II study of perioperative (12 weeks neoadjuvant and 12 weeks adjuvant) chemotherapy with mFOLFIRINOX or gemcitabine/nab-paclitaxel for resectable PDAC. Dose density (DD) was defined as the estimated percent of chemotherapy dose received of the total planned per protocol. Thresholds were based on published analyses and balance in sample size across treatment arms. Cox regression analysis of overall survival (OS) according to DD was performed in patients alive at two landmark time points: after surgery (among those who completed surgery) and at 40 weeks (when protocol therapy was to be completed). Results: Of the 103 eligible patients enrolled, median age was 64 years, 81% underwent pancreaticoduodenectomy, 15% distal pancreatectomy, and 3% a total pancreatectomy. In the 73 patients who underwent surgery, median neoadjuvant chemotherapy DD was 89%. Patients with $\geq 85\%$ DD had higher median OS from surgery (38.1 v. 17.2 months, $p = 0.039$) compared to patients with $< 85\%$ DD. Of the 82 patients who survived to 40 weeks post randomization, 67 underwent surgery and 58 started adjuvant chemotherapy. The median DD for all perioperative chemotherapy was 67%; DD was significantly higher for neoadjuvant compared to adjuvant therapy (83% vs. 58%, $p < 0.001$). In this cohort, DD $\geq 70\%$ was associated with better median OS from 40 weeks post randomization (32.2 v. 14.0 months, $p = 0.017$). DD was not significantly associated with pathologic response, margin status, or lymph node negativity. There were no significant differences in DD between the mFOLFIRINOX and gemcitabine/nab-paclitaxel arms. Conclusions: This is the first study to identify a prognostic role for chemotherapy DD in patients undergoing perioperative chemotherapy for resectable PDAC. Patients who received $\geq 85\%$ DD preoperatively and/or $\geq 70\%$ DD perioperatively had significantly higher mOS than those receiving a smaller proportion of protocol therapy. With greater survival benefit in patients who received higher chemotherapy DD, and higher DD being likelier in preoperative vs. postoperative treatment, these data support use of neoadjuvant chemotherapy for resectable PDAC. Moreover, these findings suggest that DD should be considered in prospective studies for localized PDAC to optimize therapy to be received. Research Sponsor: None.
PD-1 blockade plus chemotherapy followed by concurrent SBRT with SIB as preoperative therapy for patients with borderline resectable and locally advanced pancreatic cancer: A biomolecular exploratory, single-arm phase II clinical trial.

Juan Du, Changchang Lu, Liang Mao, Weiwei Kong, Yahui Zhu, Shanshan Shen, Qing Gu, Dongsheng Chen, Lei Wang, Yudong Qiu, Baorui Liu; The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China; Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, China; Department of Hepatopancreatobiliary Surgery, Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China; The Comprehensive Cancer Centre of Nanjing Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China; Digestive department of Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China; National Institute of Healthcare Data Science at Nanjing University, Nanjing, China; The State Key Laboratory of Translational Medicine and Innovative Drug Development, Medical Department, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing, China

Background: Pancreatic cancer is fatal malignant tumor with low resection rate and poor prognosis. We aimed to assess the safety and efficacy of a new mode of preoperative therapy for patients with locally advanced (LAPC) or borderline resectable pancreatic cancer (BRPC). Methods: This is a single arm, exploratory phase II clinical trial (ChiCTR2000032955). Gemcitabine (1000 mg/m2) and nab-paclitaxel (125 mg/m2; AG) were administered to patients with LAPC or BRPC on days 1 and 8, along with tislelizumab (200 mg) on day 1 intravenously (IV) every three weeks. Concurrently, the patients underwent stereotactic body radiotherapy (SBRT) with simultaneous integrated boost (SIB) during the third cycle of treatment. Surgical intervention was reassessed after four cycles of treatment. Objective response rate (ORR), R0 resection rate, median overall survival (mOS), median progression-free survival (mPFS) and safety were analyzed. Multiomics potential predictive biomarkers were investigated as exploratory objectives. Results: Between May 2020 and October 2021, 29 patients were enrolled in the study, 25 of them included in the intention-to-treat analysis. At the end of the last follow-up (November 30, 2022), 15 patients had a best response of partial response, the ORR was 60%. Ten patients underwent resection, and the R0 resection rate was 90% (9/10). The disease control rate (DCR) was 100%. Two of the ten resected patients achieved pathologic complete response and one patient achieved major pathological response. The mPFS, 12-months PFS rate, and 12-months OS rate were 13.7 months (95% CI: 11.7–NR), 64% (95% CI: 47.6%–85.8%), and 72% (95% CI: 56.3%–91.9%), respectively. Grade 3 or higher adverse events are anemia (8%), thrombocytopenia (8%) and jaundice (8%). Biomarker analysis indicated that patients with continuous carbohydrate antigen 19-9 decline and elevated peripheral blood eosinophil counts during treatment exhibited better survival outcomes. Furthermore, circulating tumor DNA analysis reveals that patients with a >50% decline in maximal somatic variant allelic frequency (maxVAF) between the first clinical evaluation and baseline have a longer survival outcome and higher response rate than those who are not (PFS: 20.03 vs. 10.32 months, p = 0.024; OS: not reached vs. 13.47 months, p = 0.024; ORR: 90% vs. 35.7%, p = 0.013). Moreover, maxVAF decline (> 50%) is significantly associated with the surgical rate after preoperative therapy (70.0% vs. 21.4%; p = 0.035). Conclusions: Anti-PD-1 inhibitor tislelizumab plus AG chemotherapy followed by concurrent SBRT with SIB displayed promising antitumor activity and acceptable safety profile for patients with LAPC or BRPC. Multomics potential predictive biomarkers are identified and warrant further verification. Clinical trial information: ChiCTR2000032955. Research Sponsor: National Key Research and Development Program of China (2020YFA0713804); Special Fund of Health Science and Technology Development of Nanjing (YKK20080).
Impact of positive resection margins on recurrence and survival following resection and adjuvant chemotherapy in pancreatic cancer: Results of the PRODIGE 24-CCTG PA-6 trial.

Aurélien Lambert, Julia Salleron, Alexandre Harle, James Joseph Biagi, Agnès Leroux, Jacques Thomas, Laure Monard, Jerome Cros, Frédéric Marchal, Ahmet Ayav, Thierry Conroy; Medical Oncology Department, Lorraine Cancer Institute, Nancy, France; Institut de Cancérologie de Lorraine, Vandoeuvre-Lès-Nancy, France; Institut de Cancérologie de Lorraine, Service de Biopathologie, CNRS UMR 7039 CRAN Université de Lorraine, Nancy, France; Cancer Centre of Southeastern Ontario/Queen’s University, Kingston, ON, Canada; Institut De Cancerologie De Lorraine, Vandoeuvre, France; Unicancer, Paris, France; Department of Pathology, Beaujon Hospital, APHP-INSERM U1149 Université Paris Diderot, Clichy, France; Lorraine Cancer Institute, Vandoeuvre-Lès-Nancy, France; CHRU de Nancy, Vandoeuvre-Lés-Nancy, France

Background: Pancreatic adenocarcinoma (PDAC) has a poor prognosis. Only 10-15% of patients present with resectable tumors upfront, and most patients develop recurrence and die prematurely. The data are incongruous when considering R1 status, direct invasion is not consistently a significant prognostic factor. It is recommended that 7 margins be identified for surgery: the bile duct, pancreatic neck, proximal and distal duodenum, superior mesenteric vein (SMV), superior mesenteric artery (SMA), and posterior pancreas. By analyzing data from the PRODIGE 24-CCTG PA-6 trial that validated the mFOLFIRINOX regimen in adjuvant setting, our main objective was to analyze the prognostic value of margin involvement on disease-free survival (DFS).

Methods: The protocol recommended that the surgeon inked the resection margins. R1 was defined as direct tumor margin infiltration within 1 mm of one or more resection margins. All patient data were re-evaluated centrally by an external review committee including pathologists, surgeons, and medical oncologists to verify key prognostic factors, including inking and filling of resection margins. Results: Among the 400 patients included in the study, the median number of documented margins was 6, IQR (5-7). In 214 patients (53.5%), fewer than 7 margins were reported. The most common margin involvement was on the SMV groove (28.3%), posterior margin (21%), SMA (14.5%), and pancreatic neck transection (5.3%). Margin inking was performed in 64.9% of cases. Misclassification of the R1 status concerned 24.1% of the files after centralized review. When positive, only 3 margins (SMV groove, median and posterior) were significant prognostic factors in unifactorial analysis (all p < 0.01). When combined, one R1 margin among these three had independent prognostic value in multivariable analysis. In multivariate analysis, DFS was significantly different by quality of resection margins in the gemcitabine arm (HR 95% CI 1.97 [1.23; 3.16]; p = .005) but not in the mFOLFIRINOX arm (HR 95% CI 1.46 [0.91;2.35]; p = .114).

Conclusions: Few studies have examined the prognostic implications of each margin. We consider that every effort should be made to evaluate the 3 best prognostic margins. One finding of this work is the likely effect of mFOLFIRINOX on local invasion in operated patients. It seems that this chemotherapy regimen (unlike gemcitabine) corrects the alteration related to margin involvement, probably explaining all or part of the improved survival. Therefore, the value of additional therapies, such as cloture radiotherapy, should be evaluated in patients with unknown marginal status or in those who did not benefit from mFOLFIRINOX chemotherapy. A patient who received mFOLFIRINOX as adjuvant therapy is more likely to recur with distant metastasis (80%) and with a better survival of 28 months. Clinical trial information: NCT01526135. Research Sponsor: None.
Tandem duplicator phenotype: A novel targetable subgroup in pancreatic cancer?

Abdul Rehman Farooq, Amy Zhang, Grainne M. O’Kane, Robert Edward Denroche, Gun Ho Jang, Sandra Fischer, Anna Dodd, Spring Holter, Julie Wilson, Robert C. Grant, Kyaw Lwin Aung, George Zogopoulos, Elena Elimova, Rebecca M. Prince, Raymond Woo-Jun Jang, James Joseph Biagi, Faiyaz Notta, Steven Gallinger, Jennifer J. Knox, Erica S Tsang; Princess Margaret Cancer Centre, Toronto, ON, Canada; Ontario Institute for Cancer Research, Toronto, ON, Canada; Trinity St. James’s Cancer Institute, Dublin, Ireland; University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Mount Sinai Hospital, Toronto, ON, Canada; The University of Texas at Austin, Austin, TX; McGill University Health Centre, Montreal, QC, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Princess Margaret - University Health Network, Toronto, ON, Canada; Cancer Centre of Southeastern Ontario/Queen’s University, Kingston, ON, Canada

Background: Validated biomarkers are urgently needed to provide a more precise approach in pancreatic cancer (PDAC). Homologous recombination deficiency (HRD) is a heterogenous cohort in PDAC and predicts platinum and PARP inhibitor sensitivity. The BRCA-1 genotype associates with distinct tandem duplications (TDs), however non-BRCA 1 TD phenotypes (TDP) have been observed across tumour types and may be associated with perturbations in CDK12, FBXW17, and CCNE1. Here, we characterize the prevalence and outcomes of TDP in a large series of prospectively sequenced PDAC.

Methods: Whole-genome sequencing was performed in 191 early stage resected and 275 advanced PDAC cases in the PanCuRx initiative and the COMPASS trial at the Ontario Institute for Cancer Research and Princess Margaret Cancer Centre. Tumors underwent laser capture enrichment prior to sequencing. TD scores were calculated as previously described by Menghi et al, and HRDetect scores assigned. Samples were classified as classical or basal-like by Moffitt. Outcomes of patients with TDP tumors were evaluated. Tumors that are nonHRD and nonTDP are referred to as typicals.

Results: Of 466 cases, 46 were identified as TDP (9.9%; 17 resected, 29 advanced). Subgroups of TDP by etiology included BRCA1 (n=8; 6 germline, 2 somatic), somatic CCNE1 (n=1), and unknown (n=37; no identified alterations in TDP-related genes). Pathogenic germline variants were not found in unique genes other than BRCA1. HRD TDP was associated with a significantly smaller TD size compared to nonHRD TDP (median 12 kb vs. 125 kb, p<0.0001) and median TD load of 114. NonHRD TDP genomes exhibited elevated TD load (median 70 vs. 13, p<0.0001) and HRDetect scores (p<0.0001) compared with typicals. NonHRD TDP was not prognostic in resected PDAC disease (p=0.6361) compared with typicals. We observed a trend towards improved response to 1st-line platinum therapy in nonHRD TDP vs. typicals (p=0.066) for patients with advanced disease. When stratified for only ‘classical’ RNA subtype cases as per Moffitt classification (HRD TDP:2 basal-like, 8 classical, 1 unknown; nonHRD TDP: 9 basal-like, 25 classical, 1 unknown), platinum therapy was correlated with better response in non-HRD TDP vs. typicals (n= 10, 70% ORR, p=0.0108) highlighting the chemoresistance of the basal-like subgroup. Superior survival was not observed in this small cohort.

Conclusions: In PDAC, the etiology of nonHRD TDP is unclear but may represent a potential marker for platinum and DNA damage response agents. Further investigation is warranted with a larger sample size. Research Sponsor: None.
Artificial intelligence (AI) –powered spatial analysis of tumor-infiltrating lymphocytes (TILs) for prediction of prognosis in resectable pancreatic adenocarcinoma (PDAC).

Yoojoo Lim, Jin Ho Choi, Hyemin Kim, In Woong Han, Sanghoon Song, Jiwon Shin, Heon Song, Seonwook Park, Sergio Pereira, Sang Hyun Shin, Jin Seok Heo, Kwang Hyuck Lee, Kyu Taek Lee, Jong Kyun Lee, Kee-Taek Jang, Chan-Young Ock, Joo Kyung Ock, Park; Oncology, Lunit, Seoul, South Korea; Samsung Medical Center, Seoul, South Korea; Oncology, Lunit, Seoul, Korea, Republic of (South)

Background: The degree of TIL infiltration in the tumor microenvironment has been suggested as a prognostic factor in multiple cancer types, but the significance in PDAC is not well known. The aim of this study is to assess the prognostic role of AI-based spatial TIL density assessment and immune phenotype (IP) classification in resectable PDAC.

Methods: We collected hematoxylin and eosin (H&E)-stained whole slide images (WSI) of tumor tissues and clinical data from stage I – III PDAC patients who received curative surgery at Samsung Medical Center, in Seoul, Korea, between Jan 2017 and Dec 2018. For spatial TIL analysis, we used Lunit SCOPE IO, an AI-powered pathology slide analyzer that can identify TIL and segment tumor epithelium and stroma from H&E-stained WSI. It then estimates intratumoral (iTIL) and stromal TIL (sTIL) densities, as well as IP classification of each case. IPs were defined as follows: inflamed IP (IIP) as high iTIL and sTIL; immune-excluded as low iTIL and high sTIL; immune-desert as low TIL overall. Predetermined cutoffs prior to this study were used for the determination of IPs.

Results: A total of 209 patients were identified, 182 treated with upfront surgery and 27 with preoperative chemo(radio)therapies followed by surgery. The median recurrence-free survival (RFS) and overall survival (OS) of all patients was 16.8 months (95% CI 12.1 - 21.4), and 36.8 months (95% CI 31.2 - 42.4), respectively. In the 182 patients treated with upfront surgery, the median iTIL and sTIL densities were 85.3/mm² (IQR 56.9 – 133.0) and 672.2/mm² (IQR 445.9 – 912.9). 85.7% of the cases were immune-excluded, while 11.5% were IIP. The patients having iTIL higher than the median exhibited longer RFS (HR 0.62, 95% CI 0.42 - 0.92, p = 0.017). Also, the patients having IIP exhibited longer OS (p = 0.045, HR 2.05, 95% CI 1.00 – 4.22) and a marginally longer RFS (p = 0.051, HR 2.03, 95% CI 0.98 – 4.18) compared to those with non-IIP. In the 27 patients who were treated with preoperative therapies, the iTIL densities in the surgical specimens were significantly higher compared to the 182 untreated patients (mean iTIL 168.8/mm² after chemo(radio)therapies vs. 112.6/mm² in upfront surgery, p = 0.012), although the increase in the proportion of IIP was not significant. Using the iTIL median of the 182 upfront surgery cases, 17/27(63.0%) patients had high iTIL in WSIs obtained after preoperative therapies, and these patients were observed to have a significantly better RFS (HR 0.26, 95% CI 0.09 - 0.73, p = 0.006).

Conclusions: While most cases of resectable PDAC were found to have TIL infiltration mainly in stroma, relatively higher iTIL infiltration was associated with better prognosis. An increase in iTIL after chemo(radio)therapies may be associated with better outcomes. Research Sponsor: None.
Minimally invasive versus open distal pancreatectomy for resectable pancreatic cancer (DIPLOMA): An international randomised trial.

Mohammed Abu Hilal, Maarten Korrel, Leia Jones, Jony van Hilst, Bergthor Björnsson, Ugo Boggi, Svein Olav Bratlie, Giovanni Butturini, Riccardo Casadei, Bjørn E. Edwin, Alessandro Esposito, Massimo Falconi, Bas Groot Koerkamp, Tobias Keck, Ruben de Kleine, Arto Kokkola, Daan Lips, Misha Luyer, Alessandro Zerbi, Marc G. Besselink; Istituto Ospedaliero Fondazione Poliambulanza, Brescia, Italy; Amsterdam UMC, Cancer Center Amsterdam, Amsterdam, Netherlands; Amsterdam UMC, Cancer Center Amsterdam, Amsterdam, Netherlands; Department of Surgery, Linköping University Hospital and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden; Università di Pisa, Pisa, Italy; Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden; Pancreatic Surgery Unit, Ospedale Pederzoli, Peschiera Del Garda, Italy; S. O. M.-Malpighi Hospital, Bologna, Italy; Oslo University Hospital, Oslo, Norway; General and Pancreatic Surgery Unit, Pancreas Institute, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; Pancreatic Surgery Unit, Pancreas Translational and Clinical Research Centre, Vita –Salute University, IRCCS San Raffaele Scientific Institute, Milano, Italy; Erasmus MC Cancer Institute, Rotterdam, Netherlands; University of Luebeck, Luebeck, Germany; University Medical Centre Groningen, Groningen, Netherlands; Helsinki University Hospital, Helsinki, Finland; Medisch Spectrum Twente, Enschede, Netherlands; Catharina Ziekenhuis, Eindhoven, Netherlands; Humanitas Research Hospital, Milan, Italy; Amsterdam UMC Location University of Amsterdam, Amsterdam, Netherlands

Background: In the absence of randomised trials, the oncological safety of minimally invasive distal pancreatectomy (MIDP) in patients with pancreatic cancer continues to be a matter of debate. Methods: An international randomised non-inferiority trial including patients with resectable pancreatic cancer from 35 centres in 12 countries. Patients were randomly assigned to either MIDP (laparoscopic or robotic) or open distal pancreatectomy (ODP). Both patients and pathologists were blinded to the assigned approach. Primary endpoint was radical resection (R0, <1mm free margin) in patients who had ultimately undergone resection. Analyses for the primary endpoint were by modified intention-to-treat, excluding patients who did not undergo a resection. The pre-defined non-inferiority margin was set at -7%. Results: Between May 8, 2018 and May 7, 2021, 258 patients were randomly assigned to MIDP (131 patients) or ODP (127 patients). The modified intention-to-treat population included 117 patients in the MIDP group and 114 patients in the ODP group. An R0 resection occurred in 83 (73%) patients in the MIDP group and in 76 (69%) patients in the ODP group (difference 4%, 90% CI -6 to 14%; p=0.039). Median lymph node yield was comparable (22.0 [16.0-30.0] vs 23.0 [14.0-32.0] nodes, p=0.86), as was the rate of intraperitoneal recurrence (41% vs 38%, p=0.45). Other post-operative outcomes were comparable. Conclusions: In this trial, the rate of radical resection following MIDP was non-inferior compared to ODP. This confirms the oncological validity of the minimally invasive approach in patients with resectable pancreatic cancer. Clinical trial information: ISRCTN44897265. Research Sponsor: Medtronic and Ethicon.
A phase I/II study of durvalumab and stereotactic ablative body radiotherapy (SABR) in locally advanced (LA) and borderline resectable (BR) pancreatic cancer.

Richard Tuli, Fergus Keane, Joshua David Schoenfeld, Catherine O'Connor, Charlie White, Joanne F. Chou, Carly Schwartz, Mary Larsen, Robin Brenner, Wungki Park, Nicholas Nissen, Alice Zervoudakis, Anna M. Varghese, Kenneth H. Yu, Marinela Caparu, Santosa Vardhana, Andrew Eugene Hendifar, Marsha Reyngold, Christopher H. Crane, Eileen Mary O'Reilly; USF Health Morsani College of Medicine, Tampa, FL; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY; Department of Epidemiology & Biostatistics, Memorial Sloan Kettering, New York, NY; MSKCC, New York, NY; Cedars-Sinai Medical Center, Los Angeles, CA

Background: Pancreatic cancer (PC) is largely refractory to immune checkpoint blockade (ICB) in genomically unselected patients (pts). Synergistic effects of combined ICB and radiotherapy have been suggested in varied solid tumors. Few studies have evaluated this approach in pts with PC. We sought to evaluate the safety and efficacy of PD-L1 inhibitor durvalumab (D) and SABR after induction chemotherapy, in LA and BR PC. Herein, we present phase II data from two cohorts. Methods: A multi-institutional, non-randomized phase 1/2 trial of SABR and D was conducted at Cedars-Sinai Medical Center (CS) and Memorial Sloan Kettering (MSK). Key eligibility: ECOG 0-1; unresectable PC, with stable/responding disease following 2-3 cycles gemcitabine and nab-paclitaxel (GnP) or 4-6 months (m) FOLFIRINOX (FFX). CS enrolled pts with BR and LA PC; MSK enrolled pts with LA PC only. All pts received SABR between dose 1 and 2 of D, with slight variation in ablative radiation techniques (CS: 33Gy/5#; MSK: MRI adaptive ablative radiation, 50Gy/5#). D dosed on day 1: 750mg x 4 doses Q14 days, and subsequently Q2 or Q4 weeks x 1 year total, or until resection, progression of disease (POD), or limiting toxicity. Primary endpoint: 6-month progression free survival (6 m PFS). Secondary endpoints: rate of downstaging to resectability, objective response by RECIST v1.1, duration of response, PFS, Overall Survival (OS). PFS and OS estimated from consent date using Kaplan-Meier method. Association between surgery and outcomes was analyzed as a time dependent covariate in univariate Cox regression models for OS and PFS. To assess immunogenomic biomarkers of response, pre- and on-treatment tissue, blood and microbiome samples were gathered. Results: Between 08/2017 and 05/2022, N= 36 enrolled. Median age 67.5 years (range 48-79), 39% (14/36) female. Performance Status: N=12 (33%) ECOG 0; N= 24 (67%) ECOG 1. Median duration chemotherapy: 3.5 m (range 1.4, 5.8). Staging: N=31 (86%) LA; N=5 (14%) BR. N=9 (25%) underwent resection; all R0. Conversion to resection was not associated with PFS (HR 0.45; 95% CI 0.17, 1.17, p=0.1) or OS (HR 0.69; 95% CI 0.26, 1.84, p=0.5). Survival and response data summarized in table. Toxicities of special interest: Grade 3 treatment-related: in N= 7; diarrhea N= 2; elevated AST/ALT N= 2; lipase/amylase elevation, N=1; nausea N=1. Grade 4: amylase elevation N=1. Conclusions: D and SABR after induction chemotherapy in LA and BR PC is safe, had an encouraging 6-m PFS of 69% and favorable RO resection rate, warranting further evaluation. Immuno-genomic biospecimen analyses underway. Clinical trial information: NCT03245541. Research Sponsor: AstraZeneca.

<table>
<thead>
<tr>
<th>Median Follow-Up (95% CI)</th>
<th>23 m (18, -)</th>
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<tbody>
<tr>
<td>6-m PFS (95% CI)</td>
<td>69% (56%, 86%)</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>8.2 m (6.1, 14)</td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>17 m (13, -)</td>
</tr>
<tr>
<td>Best Objective Response</td>
<td>Complete Response: 1 (3%)</td>
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<tr>
<td></td>
<td>Partial Response: 10 (28%)</td>
</tr>
<tr>
<td></td>
<td>Stable Disease: 23 (4%)</td>
</tr>
<tr>
<td></td>
<td>POD: 2 (6%)</td>
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</table>
Meta-analyses of factors associated with long-term survival after resection of pancreatic ductal adenocarcinoma.

Asad Saulat Fatimi, Ammar Asrar Javed, Omar Mahmud, Alyssar Habib, Mahip Grewal, Jin He, Christopher Lee Wolfgang, Marc G. Besselink; Aga Khan University, Karachi, Pakistan; NYU Langone Medical Center, New York, NY; The Aga Khan University, Karachi, Pakistan; University of Maryland School of Medicine, Baltimore, MD; NYU Langone Health, New York, NY; Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Surgery, New York University School of Medicine and NYU-Langone Medical Center, New York, NY; Amsterdam UMC Location University of Amsterdam, Amsterdam, Netherlands

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies. Long-term survival (>5 years, LTS) is rarely seen even after 'curative-intent' resection. With improved systemic control via effective systemic therapies, LTS is now being reported more frequently. However, our understanding of LTS in PDAC remains limited. The aim of the current study was to perform a systematic review and meta-analysis to quantify the associations between various clinicopathological factors and LTS following resection of PDAC. Methods: The PubMed, Embase, Scopus, and Cochrane CENTRAL databases were systematically searched for articles reporting actual patient survival data. Two reviewers independently screened and reviewed articles, extracted relevant data, and assessed the risk of bias in included studies using the Newcastle-Ottawa scale (NOS). Data that compared patients who achieved LTS after resection with those who did not were extracted from the included studies. Meta-analyses using a random effects model were conducted to identify associations between LTS and various patient, tumor, and treatment related factors. Results: Overall, 33 studies with 46,981 patients after resection of PDAC were included. Most articles received a 'good' NOS assessment, indicating acceptable risk of bias. The median rate of LTS was 15.27% (IQR: 9.47-20.72). Multiple clinicopathological factors were found to be associated with LTS, including tumor grade (OR: 0.40, 95%CI: 0.31-0.52), tumor stage (OR: 0.36, 95%CI: 0.31-0.41), and margin status (OR: 0.43, 95%CI: 0.36-0.50). Factors that were not associated with LTS included patient age, tumor size, tumor location, or genetic mutations. Notably, adjuvant therapy (OR: 1.68, 95%CI: 1.24-2.28) but not neoadjuvant therapy (OR: 1.08, 95%CI: 0.62-1.87) were associated with LTS. Conclusions: This meta-analysis revealed that 15% of patients achieved LTS after resection of PDAC. Multiple clinicopathological factors are associated with LTS whereas presence of ‘traditional’ negative prognostic factors does not rule out LTS. Further studies are required to identify robust predictors of LTS in resected PDAC. Research Sponsor: None.

Clinicopathological characteristics associated with LTS in resected PDAC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1.29 (1.01, 1.64)</td>
</tr>
<tr>
<td>Pathologic T-stage</td>
<td>0.40 (0.31, 0.52)</td>
</tr>
<tr>
<td>Pathologic M-stage</td>
<td>0.16 (0.06, 0.38)</td>
</tr>
<tr>
<td>Nodal Disease</td>
<td>0.40 (0.35, 0.45)</td>
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<tr>
<td>Vascular Invasion</td>
<td>0.50 (0.39, 0.64)</td>
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<tr>
<td>Perineural Invasion</td>
<td>0.45 (0.29, 0.69)</td>
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<tr>
<td>Lymphatic Invasion</td>
<td>0.44 (0.32, 0.60)</td>
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<tr>
<td><strong>Tumor Factors</strong></td>
<td></td>
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<tr>
<td>Major Vessel Resection</td>
<td>0.62 (0.41, 0.93)</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>1.68 (1.24, 2.28)</td>
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</tbody>
</table>
Mutation-site localized non-B DNA burden and survival heterogeneity in early-stage pancreatic cancer.

Qi Xu, Jeanne Kowalski-Muegge; Livestrong Cancer Institutes, University of Texas at Austin, Austin, TX; Livestrong Cancer Institutes, The University of Texas at Austin Dell Medical School, Austin, TX

Background: Pancreatic cancer is a highly aggressive disease with a poor prognosis, and one in which most measure of genomic instability (e.g., tumor mutation burden (TMB), fraction of genome altered (FGA)) have thus far, not proven informative in differentiating survival. Non-B DNA are alternative DNA forms that deviate from the canonical B-DNA structure with potential to increase susceptibility to mutations, leading to the development of cancer. The role of non-B in pancreatic cancer has not been fully explored. Herein, we investigate the relationship between gene mutation sites co-localized with non-B DNA motifs in terms of survival and B-DNA features. Methods: Using TCGA data, we derived a genome-wide mutation signature on 104 early-stage pancreatic patients. We introduced a metric, mutation-localized non-B burden (MLNB) by the number of non-b motifs containing mutation sites, normalized to the number of mutations and motif library size. We applied MLNB to patient-specific mutation signatures to derive an MLNB burden for non-B DNA structure motifs: G-quadruplexes (G4), Z-DNA, inverted repeats (IR), mirror repeats (MR), direct repeats (DR), and short tandem repeats (STR). We performed a cluster analysis on MLNB and compared groups based on overall survival (OS) in months (mos) using a log-rank test. Comparisons of B-DNA-derived molecular features among clusters were performed using a Kruskal-Wallis and Fisher Exact test. Results: Among the 104 early-stage pancreatic patients with a mutation signature, MLNB clustering resulted in six patient clusters that differentiated by non-B DNA structure, with DR burden the longest OS cluster (n=23, median OS=30mos), significantly (p < 0.05) differing as compared to IR (n=23, median OS=15 mos), STR (n=20, median OS=16mos), MR with lack of IR (n=14, median OS=13mos) and MR with IR (n=16, median OS=8mos). A mix of Z-DNA and G4 burden defined a cluster with shorter OS (n=22, median OS=14mos) as compared to DR, though not significant. Patients with the longest OS, MLNB-DR burden cluster had mutation signatures enriched in MAPK and Notch signaling pathways, as compared to the other clusters enriched with double-stranded break and mismatch repair (IR), hedgehog and WNT signaling (STR), and interleukin-4 signaling (MR) pathways. Among all clusters, CDKN2A deletion was most prevalent except for MLNB-DR burden cluster. No Significant differences were found between the MLNB clusters with age, race gender, KRAS and TP53 mutations, FGA, TMB, tumor purity, Bailey and Moffit subtypes. Conclusions: Our results point towards the potential use of MLNB as an emerging marker of site-structure genomic instability. Considering that triplex DNA is emerging as a marker genomic instability, and that we distinguish between two MR groups based on IR burden, our results may provide insights into various instability mechanisms associated with poor survival in pancreatic cancer. Research Sponsor: University of Texas Dell Medical School.
The five periampullary cancers: Not just different siblings but different families—An international multicenter cohort study.

Bas Uijterwijk, Santiago Cabus, Vasileios K. Mavroeidis, Patrick Pessaux, Dimitris Korkolis, Adam C. Berger, Bergthor Björnsson, Miguel Suárez, Miljama Vladimirov, Jorg Kleeff, Ugo Boggi, Zahir Soonawalla, Alberto Zaniboni, Mario Serradilla, Michele Mazzola, Poya Ghorbani, Ulrich Wellner, Marc G. Besselink, Mohammed Abu Hilal; Fondazione Poliambulanza Istituto Ospedaliero 57, Brescia, Italy; Hospital de Sant Pau, Barcelona, Spain; Royal Marsden, London, United Kingdom; Department of General, Digestive, and Endocrine Surgery, Nouvel Hôpital Civil, Strasbourg, France; Hellenic Anticancer Hospital 'Saint Savvas', Athens, Greece; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Linköping University Hospital, Linköping, Sweden; University Hospital Virgen de la Victoria, Malaga, Spain; Klinikum Nürnberg, Nurnberg, Germany; Martin-Luther University Halle-Wittenberg, Halle, Germany; Università di Pisa, Pisa, Italy; Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; CdC Poliambulanza, Brescia, Italy; Miguel Servet University Hospital, Zaragoza, Spain; ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; Karolinska University Hospital, Stockholm, Sweden; University Hospital Schleswig-Holstein, Campus Luebeck, Lübeck, Germany; Amsterdam UMC Location University of Amsterdam, Amsterdam, Netherlands; Istituto Ospedaliero Fondazione Poliambulanza, Brescia, Italy

Background: Cancer arising in the periampullary region can be anatomically classified in pancreatic ductal adenocarcinoma (PDAC), distal cholangiocarcinoma (dCCA), duodenal adenocarcinoma (DAC) and ampullary adenocarcinoma (AAC). Based on histopathology, the AAC is currently subdivided in the intestinal (AmpIT) and pancreatobiliary (AmpPB) subtype. Despite close anatomical resemblance, it is unclear how the ampullary subtypes relate to the remaining periampullary cancers in tumor characteristics and behavior.

Methods: This is an international multicenter cohort study, including patients after curative intent resection for periampullary cancer retrieved from 45 centers (from Europe, USA, Asia and Canada) between 2010 and 2021. Pre-operative CA19-9, differences in pathology and postoperative pancreatic fistula (POPF, grade B/C), 8-year overall survival (OS) and disease-free interval (DFI) were compared between DAC, AmpIT, AmpPB, dCCA and PDAC. Results: Overall, 3809 patients were included of which 348 DAC, 774 AmpIT, 848 AmpPB, 1036 dCCA and 803 PDAC. The best 8-years overall survival was found in patients with AmpIT and pancreas-related (AmpPB and PDAC). The best tendency was found between AmpIT and PDAC (49.8% and 47.9%), followed by AmpPB (34.9%, p<0.001), dCCA (26.4%, p=0.020) and last, PDAC (12.9%, p<0.001). The best 8-years DFI was measured for AmpIT (62.7%) and the worst for both dCCA and PDAC (24.9% and 21.8%). This pattern correlated with the height of the pre-operative CA19-9 but not with the pathology, in which the largest and most progressed tumors were found in DAC. The incidence of POPF was lower in the pancreas-related tumor types (AmpPB 18.5%, PDAC 8.3%) compared to the non-pancreas related types (DAC 27.3%, AmpIT 25.5%, dCCA 27.6%). Conclusions: Despite the close anatomic relation of the five periampullary cancers, this study shows that there are prognostic and clinically relevant differences in terms of preoperative blood markers, pathology, complications, long-term survival, and recurrence. More characteristics are shared between DAC and AmpIT and between AmpPB and dCCA than between the two ampullary subtypes. Instead of using collective definitions for “periampullary cancers”, this study emphasizes the need for individual evaluation of each histopathological periampullary subtype with the ampullary subtypes as individual entities in future studies.

Research Sponsor: None.

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Incidence, epidemiological characteristics, and cause-specific survival analysis of ampullary carcinoma using the SEER database.

Rajvi Gor, Pranav Gwalani, Dhairya Gor, Twinkle Gwalani, Hibai Narvel, Charan Thej Reddy Vegivinti, Sudhamsh Desai, Fnu Vikash, Sindhu Vikash, Hasiy Yuuf, Abhishek Kumar; Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY; Icahn School of Medicine at Mount Sinai, New York, NY; Jersey Shore University Medical Center, Neptune City, NJ; Gujarat Cancer Society Medical College, Hospital and Research Center, Ahmedabad, India; Jacobi Medical Center/AECOM, Bronx, NY; Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY; Albert Einstein College of Medicine, Jacobi Medical Center, Bronx, NY; Jacobi Medical Center, Bronx, NY

Background: Ampullary carcinomas (AC) are rare and comprise only 0.2% of gastrointestinal malignancies, and there is a paucity of studies analyzing them. We studied the incidence, demographics, tumor characteristics, and survival variables of patients with AC using the Survival, Epidemiology, and End Results [SEER] November 2021 database. Methods: We identified 3650 patients aged >18 with microscopically confirmed adenocarcinoma of the ampulla using ICD-O-3 site code C241 and histology codes (8140-8147, 8480, 8490, 8500). The epidemiological characteristics and the survival variables included were age, gender, ethnicity, and American Joint Committee on Cancer [AJCC] Staging. The overall 5-year survival (OS), cause-specific 5-year survival (CSS), and CSS plots across different strata were plotted using the Kaplan-Meier Method. The analysis was done using the Cox proportional hazard regression model (p<0.05). Results: The overall age-adjusted incidence of AC was 0.3 per 100,000 cases. The median age at diagnosis was 69 (Interquartile range - 59, 78). It was more common in males (56.03%) and Non-Hispanic White (58.96 %), with the most common stages at a presentation being stage 2B IIB (22.08%) and stage III (22.11%). The observed overall 5-year survival was 31%, and the cause-specific 5-year survival was 37.5%. The CSS was not significantly associated with gender (p=0.06). The estimated hazards of death attributed to AC increase by 13% (p < 0.0001) for every 10-year increase in age at diagnosis above 67 years. The CSS was also associated with race, with African Americans and Hispanics being associated with higher hazards of death attributed to AC when compared to Non-Hispanic Whites with HR of 1.5 (p<0.0001) and 1.12 (p=0.01), respectively. Conclusions: Ampullary carcinoma is more commonly seen in males and non-Hispanic Whites with a median age of 69 years. Patients are typically diagnosed in stages IIB and III. Lower CSS rates were associated with advancing age, African American, and Hispanic populations. We need further studies to determine whether these disparities between different races are due to socioeconomic, genetic, or biological factors. Additional studies investigating how different treatment options affect AC survival, especially in this population subset, can be explored. Research Sponsor: None.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Patients (n=3650)</th>
<th>Hazard Ratio (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Median (IQR)</td>
<td>69 (59.78)</td>
<td>1.013 (&lt;0.0001)</td>
</tr>
<tr>
<td>Sex, Male, N (%)</td>
<td>2045 (56.03)</td>
<td>1.11 (0.06)</td>
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<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
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<tr>
<td>Non-Hispanic White</td>
<td>2152 (58.96)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>688 (18.85)</td>
<td>1.12 (0.01)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>280 (7.67)</td>
<td>1.52 (&lt;0.001)</td>
</tr>
<tr>
<td>Non-Hispanic Asian</td>
<td>500 (13.70)</td>
<td>1.07 (0.39)</td>
</tr>
<tr>
<td>Non-Hispanic American Indian</td>
<td>21 (0.58)</td>
<td>1.11 (0.80)</td>
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<tr>
<td>Stage</td>
<td></td>
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<tr>
<td>IA</td>
<td>473 (12.96)</td>
<td>1.0</td>
</tr>
<tr>
<td>IB</td>
<td>462 (12.66)</td>
<td>1.08 (0.39)</td>
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<tr>
<td>IIA</td>
<td>363 (9.95)</td>
<td>1.0 (0.88)</td>
</tr>
<tr>
<td>IIB</td>
<td>856 (22.09)</td>
<td>1.17 (0.07)</td>
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<tr>
<td>III</td>
<td>807 (22.09)</td>
<td>1.09 (0.38)</td>
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<td>IV</td>
<td>419 (11.48)</td>
<td>1.20 (0.28)</td>
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<td>UNK</td>
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Detection and localization of gastrointestinal cancers based on multi-dimensional signatures from a single cfDNA targeted sequencing assay.

Xin-Rong Yang, Dong-Li He, Zhi-Guo Xiong, Bin Yan, Quan-Lin Li, De-Zhen Guo, Ao Huang, Zhen Feng, Pin-Xiang Lu, Qi Guo, Meng-Jiang He, Wei-Zhong Chen, Qi-Ye He, Zhi-Xi Su, Rui Liu, Yunshi Zhong, Jia Fan, Jian Zhou; Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University; Key Laboratory of Carcinogenesis and Cancer Invasion (Fudan University), Ministry of Education, Shanghai, China; Department of Gastroenterology, Xuhui Central Hospital, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Gastrointestinal Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Clinical Laboratory, Qingpu Branch of Zhongshan Hospital, Fudan University, Shanghai, China; Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, Shanghai, China; Department of General Surgery, Xuhui Central Hospital, Shanghai, China; Endoscopy Center, Xuhui Central Hospital, Zhongshan Hospital, Fudan University, Shanghai, China; Singlea Genomics Ltd., Shanghai, China; Liver Cancer Institute, Zhongshan Hospital, and Key Laboratory of Carcinogenesis and Cancer Invasion (Ministry of Education), Fudan University, Shanghai, China

Background: Five major gastrointestinal (GI) cancers - colorectal (CRC), gastric (GC), liver (LC), esophageal (EC), and pancreatic cancer (PC) - are responsible for hundreds of thousands of mortalities annually worldwide. Unfortunately, there is a lack of cost-effective, blood-based screening method for their early detection. To address this issue, we aimed to develop GutSeer, a non-invasive, targeted methylation sequencing-based test by leveraging methylation and fragmentomic signatures carried by cell-free DNA (cfDNA).

Methods: The panel of GutSeer consists of 1656 target regions which were either differentially methylated between healthy and cancer samples, or distinctively methylated in a specific GI cancer. Cancer and healthy participants were recruited and randomly divided into a training and a validation cohort. Their plasma DNA samples were analyzed to generate DNA methylation and fragmentomic features. These multi-dimensional features were integrated to build ensemble stacked machine learning models to differentiate cancer against healthy, and to determine the tissue-of-origin (TOO) of the cancer.

Results: A total of 1844 cases (787 healthy, 342 LC, 239 GC, 209 EC, 180 CRC, and 87 PC cases) were recruited for this study. A cancer-vs-healthy model achieved an AUC of 0.94 and 0.95 (sensitivity of 77.7% and 77.1% under the specificity around 96%) using either methylation or fragmentomic features only, respectively. Combining both methylation and fragmentomic features further improved performances, achieving an AUC of 0.96 (sensitivity = 86.2% at a specificity of 96.7%). For individual type of cancer, GutSeer has a sensitivity of 93.3% for CRC, 81.1% for EC, 70.3% for GC, 96.5% for LC, and 86.4% for PC. An independent test using 629 benign cases as controls achieved a specificity of 87.1%. A separate TOO model was built using all features and achieved an overall accuracy of 82% for all cancer cases (66.7% for CRC, 87.0% for GC and EC combined, 89.0% for LC, and 63.2% for PC). Same as the cancer detection model, using multi-dimensional features in TOO prediction yielded higher accuracy than when models using only methylation or fragmentomics features (accuracy = 75.6% or 75.4%, respectively). When compared with whole-genome sequencing (WGS) based approaches, GutSeer showed a comparable performance in cancer detection but a higher accuracy in TOO identification, further confirming its effectiveness for detection of GI cancers.

Conclusions: GutSeer, a non-invasive test integrating multi-dimensional features, was demonstrated to detect and localize the 5 main types of GI cancer with high accuracy. Our results further showed that a reasonably sized panel can perform comparably or even better than WGS-based methods in cancer detection and TOO localization, indicating GutSeer may be a low-cost solution for blood-based early screening for GI cancers. Research Sponsor: National Key Research and Development Program of China (2019YFC1315800).
Multi-institutional study evaluating the role of circulating tumor DNA (ctDNA) in management of appendiceal cancers (AC).

Erika Belmont, Varun Vivek Bansal, Mohammad A. A. Zeineddine, Michael White, Blase N. Polite, Chih-Yi Liao, Oliver S. Eng, Kiran Turaga, John Paul Y.C. Shen, Ardaman Shergill; University of Chicago Medical Center, Chicago, IL; Department of Surgery, Section of Surgical Oncology, University of Chicago Medical Center, Chicago, IL; University of Texas MD Anderson Cancer Center, Houston, TX; University of Chicago, Chicago, IL; Department of Surgery, University of California, Irvine, Orange County, CA; Department of Medicine, Section of Hematology and Oncology, University of Chicago, Chicago, IL

Background: AC frequently present with peritoneal metastases (PM) which are difficult to accurately measure with imaging techniques or serum tumor markers. ctDNA is a novel, promising biomarker to assess minimal residual disease (MRD) and therapy response. Its utility in AC with PM is poorly studied due to the rarity of this disease condition. This is a report on the role of ctDNA in AC management.

Methods: Patients with AC managed at two high volume centers between 01/01/2019 to 12/15/2022 were included in this study. CtDNA measurements were prospectively collected using Signatera tumor informed ctDNA assay during clinical care and these data were abstracted retrospectively. Cox-proportional hazards were utilized for survival analysis.

Results: 97 patients with AC were included with a median age of 57 (IQR 53-66) years, majority being non-Hispanic white (85%) and female (63%). 68 (70%) patients had ctDNA assay drawn at the time of confirmed clinical disease (radiographic or laparoscopic). The sensitivity of ctDNA was 56% (CI 44% - 67%) for all grades, and 66% (CI 49% - 80%) for grade 3 tumors. 65 (67%) patients underwent cytoreductive surgery (CRS), of which 16 (24.6%) had preoperative ctDNA assays. Sensitivity in this cohort of surgical patients was 25% and positive ctDNA showed poor correlation with PCI score at time of surgery (n=4, r = 0.38, p = 0.14). Any positive value for post-operative ctDNA was associated with lower disease free survival (DFS) (9 months (CI 5-13) in low grade AC and 10 months (CI 7-14) in high grade AC, compared to not reached for those persistently negative (p<0.001) over a median follow-up duration of 17 months. This difference persisted despite adjusting for adjuvant chemotherapy for high-grade disease (aHR = 11.2 (1.4-88.6), p = 0.023).

Conclusions: This is the largest study reported to date of tumor informed ctDNA testing in patients with AC. These data show that ctDNA has low sensitivity in both the metastatic unresectable and in pre-operative settings. However, ctDNA positivity after CRS in AC has prognostic value and could be used to guide systemic therapy decisions. Research Sponsor: None.
A phase 2 trial of chemotherapy, pembrolizumab, and propranolol in patients with advanced esophageal/gastroesophageal junction adenocarcinoma (EGAC).

Sarbajit Mukherjee, Karan Jatwani, Sarah Chatley, Christos Fountzilas, Sylvia Vania Alarcon Velasco, Deepak Vadehra, Renuka V. Iyer, Kristopher Atwood, Mark Farrugia, Anurag K. Singh, Elizabeth A. Repasky; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Division of GI Medicine, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Roswell Park Cancer Institute, Buffalo, NY

Background: Chronic stress suppresses the immune system and promotes cancer cell growth. In animal studies, we reported that this is mediated by the beta-adrenergic (BA) pathway. We further showed that concurrently blocking the BA pathway with β-blockers (BB) can improve immune checkpoint inhibitor (ICI) efficacy. Our retrospective data analysis revealed that esophageal cancer (EC) patients taking BB for other non-cancer reasons while receiving chemoradiation had significantly better survival and distant control than those not taking BB. We hypothesized that blocking the effects of adrenergic stress with a commonly used BB, propranolol, will improve response to therapies in EC patients.

Methods: This is an open-label, non-randomized, phase 2 study of propranolol combined with pembrolizumab and standard chemotherapy in frontline unresectable/metastatic EGAC. Eligible patients must be treatment-naive, have adequate organ function, have an ECOG performance status of 0–1, and be able to swallow and retain oral medication. Patients with Her-2 positive cancer, active autoimmune disease, active HIV, Hepatitis B or C, or a history of non-infectious pneumonitis/interstitial lung disease that requires treatment, are ineligible. Patients who are on BB for various indications are also ineligible. Eligible patients will receive mFOLFOX6 every two weeks in combination with pembrolizumab 400 mg intravenously every six weeks and propranolol 30 mg orally twice daily. The mFOLFOX6 dosing regimen will consist of 5-FU 400 mg/m2 and oxaliplatin 85 mg/m2 followed by bolus 5-FU 400 mg/m2 and a 48-hour infusion of 5-FU 2400 mg/m2. The study will include an initial safety lead-in cohort of six patients. The primary endpoint is the overall response rate (ORR) determined by RECIST 1.1. Secondary endpoints include safety, progression-free survival (PFS), overall survival (OS), and ORR as determined by iRECIST. Correlative studies will assess baseline levels or changes in the levels of biomarkers, like, peripheral T-cell subsets/myeloid-derived suppressor cells (MDSC)/cytokines/ and perceived stress scale PSS/chronotropic effects of exercise with efficacy (ORR, PFS, OS). Assuming a historic ORR of 50% with standard treatment, 37 evaluable pts are needed to show a 20% increase in ORR with our proposed treatment with 80% power at a one-sided significance level of \( \alpha = 0.1 \). In stage 1, \( n_1 = 23 \) evaluable pts will be enrolled. If there are 13 or more ORRs, an additional \( n_2 = 14 \) pts will be enrolled in stage 2. If 24 or more ORRs are observed in the total \( n = 37 \) evaluable pts, the proposed treatment regimen will be considered promising for further study. The study is currently open to enrollment. Clinical trial information: NCT05651594. Research Sponsor: Department of Defense CA210898P1; Roswell Park Comprehensive Cancer Center internal funding.
Chemoradiotherapy with concurrent durvalumab for the palliative treatment of oligometastatic esophageal and gastroesophageal carcinoma with dysphagia: A single arm phase 2 clinical trial, PALEO.

Fiona Day, Swetha Sridharan, Michael Michael, Louise Christophersen, Melissa M. Moore, Melissa A. Eastgate, Stephen Thompson, ANGELA MWEEMPWA, Christopher Oldmeadow, Allison Fraser, Jarad Martin; Department of Medical Oncology, Calvary Mater Newcastle, Waratah, Australia; Calvary Mater, Newcastle, Australia; Peter MacCallum Cancer Centre, Melbourne, Australia; Australasian Gastro-Intestinal Trials Group, Sydney, Australia; St. Vincent’s Cancer Centre, Fitzroy, Australia; Royal Brisbane and Women’s Hospital, Herston, Australia; Prince of Wales Hospital, Randwick, Australia; Regional Cancer and Blood Centre, Auckland District Health Board, Auckland, New Zealand; Hunter Medical Research Institute, Newcastle, Australia; Calvary Mater Newcastle, Newcastle, Australia

Background: Many patients diagnosed with esophageal cancer have dysphagia from their primary tumor and de novo metastatic disease. While multiple therapies are available, there is no accepted standard or sequence of therapies to both relieve dysphagia and control distant disease. Our preceding Phase I clinical trial showed that a 2 week hypofractionated chemoradiotherapy (CRT) protocol (30Gy/10# with concurrent weekly carboplatin and paclitaxel) is well tolerated and provides rapid dysphagia relief. Immune checkpoint inhibition has activity in esophageal and gastroesophageal (GEJ) cancer and concurrent radiotherapy may improve T cell priming through tumor antigen release. In PALEO, patients begin durvalumab concurrent with primary tumor CRT, and receive stereotactic body radiotherapy (SBRT) (24Gy/3#) to a single metastasis to maximize the breadth of tumor antigen exposure. Tissue and blood-based studies are planned to identify biomarkers for response, including immunosequencing to test for post-radiotherapy expansion in T cell receptor diversity. Methods: Eligible patients have biopsy-proven esophageal or GEJ cancer, either squamous cell or adenocarcinoma histology, with oligometastatic (1-5 metastases on FDG-PET scan outside the primary tumor radiotherapy field) or locoregionally advanced disease unsuitable for surgery, dysphagia (Mellow score 0), and ECOG PS 0-2. Key exclusion criteria are prior treatment, tumor HER2 positivity, prior thoracic radiotherapy, tracheoesophageal fistula, esophageal stent in situ and contraindications to immunotherapy. Patients begin durvalumab 1500mg q4w with CRT to the primary tumour (30Gy/10# with weekly carboplatin AUC2 and paclitaxel 50mg/m2), and continuing to disease progression, unacceptable toxicity or 2 years. SBRT to one metastasis (24Gy/3#) is delivered in week 7. Trial primary endpoint is progression free survival rate at 6 months (PFS6) with the aim to rule out a PFS6 rate of 50% in favor of 67.5%, with 80% power and a one-sided 0.05 significance level. Secondary endpoints include dysphagia relief, nutritional status change (patient weight, removal of enteral feeding tubes, PG-SGA score), quality of life, response rate, toxicity, overall survival and exploratory translational endpoints. PALEO is sponsored by the Australasian Gastro-Intestinal Trials Group (AGITG) for conduct at 8 sites in Australia and New Zealand. 6 of planned 54 patients have been enrolled. Clinical trial information: ACTRN12619001371189. Research Sponsor: Australasian Gastro-Intestinal Trials Group (AGITG) Philanthropic Major Donor funding; Hunter Medical Research Institute; This research was conducted with Study Drug support from AstraZeneca PtyLtd; Varian Medical Systems.
Phase 2 trial of zolbetuximab in combination with mFOLFOX6 and nivolumab in patients with advanced or metastatic claudin 18.2-positive, HER2-negative gastric or gastro-esophageal junction adenocarcinomas.

Kohei Shitara, Kensei Yamaguchi, Hirokazu Shoji, Maria Matsangou, Pranob P. Bhattacharya, Jung Wook Park, Samuel J Klempner; Department of gastroenterology and gastrointestinal oncology, National Cancer Center Hospital East, Kashiwa, Japan; The Cancer Institute Hospital of JFCR, Tokyo, Japan; Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Chuo City, Tokyo, Japan; Astellas Pharma Global Development, Inc., Northbrook, IL; Mass General Cancer Center, Boston, MA

Background: Zolbetuximab, a chimeric immunoglobulin G1 monoclonal antibody, binds to claudin 18.2 (CLDN18.2) and mediates tumor cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In the pivotal phase 3 SPOTLIGHT study, zolbetuximab with modified FOLFOX6 (mFOLFOX6; leucovorin [folinic acid], fluorouracil [5-FU], and oxaliplatin) significantly prolonged progression-free survival (PFS) and overall survival (OS) in patients with CLDN18.2-positive, HER2-negative gastric and gastroesophageal junction (G/GEJ) adenocarcinomas. The phase 2 ILUSTRO trial is investigating the efficacy and safety of zolbetuximab, alone and in multiple combinations, in patients with CLDN18.2-positive, HER2-negative advanced/metastatic G/GEJ adenocarcinomas.

Methods: The ILUSTRO trial is enrolling two new cohorts, 4A (safety cohort) and 4B, with approximately 12 and 50 patients planned, respectively, to assess safety and efficacy of the first-line combination of zolbetuximab, mFOLFOX6, and nivolumab in G/GEJ adenocarcinomas. Both cohorts are enrolling patients whose tumors are HER2-negative with high or intermediate CLDN18.2 positivity (moderate to strong immunohistochemistry staining intensity in $\geq75\%$ of tumor cells [high] or $\geq50\%$ but $<75\%$ of tumor cells [intermediate]). In Cohort 4A, patients will receive a loading dose of 800 mg/m² of zolbetuximab with 240 mg of nivolumab and mFOLFOX6 on cycle 1 day 1, followed by 400 mg/m² of zolbetuximab with 240 mg of nivolumab and mFOLFOX6 every 2 weeks (on days 15 and 29 of each 42-day cycle). Up to 12 mFOLFOX6 treatments (4 cycles) will be administered; patients may continue to receive folinic acid and 5-FU alongside zolbetuximab and nivolumab. Tolerability and safety of the combination of zolbetuximab, mFOLFOX6, and nivolumab will be evaluated during a 2-week dose-limiting toxicity assessment period. If the 800 mg/m² loading dose of zolbetuximab was assessed as not tolerable, patients were to be de-escalated to 600 mg/m² as their loading dose but received the same subsequent 400 mg/m² doses of zolbetuximab every 2 weeks. Cohort 4B will receive this combination at the dose level determined in Cohort 4A. Efficacy endpoints include objective response rate, disease control rate, duration of response, PFS, and OS. Safety and tolerability, pharmacokinetics, immunogenicity, and health-related quality of life will also be evaluated. Currently, 20+ sites are recruiting in 6 countries (France, Italy, Japan, Korea, Taiwan, United States); more US sites are planned. Clinical trial information: NCT03505320. Research Sponsor: Astellas Pharma, Inc.

Andrew H. Ko, Mark Zalupski, Raed Moh’d Taiseer Al-Rajabi, Khalid Matin, Deirdre Jill Cohen, Smitha S. Krishnamurthi, Brent Kreider, Jessica A. Box, Caroline Emery, Martin Teresk, Mary Laura Varteresian, Martin Lee, Anna Groover, Deb Knoerzer, Rachna T. Shroff; University of California San Francisco, San Francisco, CA; University of Michigan, Ann Arbor, MI; University of Kansas Medical Center, Kansas, KS; Massey Cancer Center, Virginia Commonwealth University, Richmond, VA; Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; Cleveland Clinic, Cleveland, OH; BioMed Valley Discoveries, Inc., Kansas City, MO; Independent Consultant, Ann Arbor Drug Safety, LLC, Ann Arbor, MI; Biomed Valley Discoveries, Kansas City, MO; University of Arizona Cancer Center, Tucson, AZ

Background: RAS-induced signaling through the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway plays an important role in the pathogenesis of many solid tumors. Ulixertinib (BVD-523) is a first-in-class and best-in-class small molecule inhibitor of ERK 1/2 that is currently being investigated in multiple cancer clinical trials, both as a single agent and as part of combination therapy. Preclinical studies have demonstrated that inhibition of the RAS/MAPK/ERK signaling cascade leads to upregulation of autophagy, a catabolic pathway that includes the lysosomal degradation of proteins to support cellular metabolism during times of cellular stress. Given cancer cells’ increased reliance on autophagy to enhance their survival in this context, this study seeks to evaluate the combination of ulixertinib with hydroxychloroquine, an antimalarial drug known to suppress autophagy, in patients with advanced gastrointestinal malignancies harboring mutations in genes involved in MAPK signaling. Methods: This is an open-label, multicenter, phase II basket study of ulixertinib in combination with hydroxychloroquine in patients with advanced GI malignancies harboring mutations in one of the following MAPK signaling-associated genes: KRAS, NRAS, HRAS, BRAF (non-V600), MEK1/2, or ERK1/2. The completed Phase 1 dose-escalation trial (NCT04145297) established the recommended Phase 2 dose which will be the doses used in this study; ulixertinib 450mg PO BID combined with hydroxychloroquine 600mg PO BID, both drugs administered daily in 28-day cycles, with tumor assessments after every 2 cycles. The trial has five baskets based on primary disease: cholangiocarcinoma, pancreatic adenocarcinoma, colorectal adenocarcinoma, esophageal adenocarcinoma, and gastric adenocarcinoma. A Simon two-stage design will be employed within each of the 5 disease-specific baskets noted above, with the first stage of enrollment consisting of n=13 patients/basket. To be considered evaluable, a patient must complete at least one cycle of therapy and receive at least 75% of the prescribed dose during that first cycle. If ≥4 patients in a specific basket achieve a response (complete or partial), that basket will then open to Stage 2 with enrollment of an additional 30 patients. Primary study endpoints will include safety/toxicity as well as ORR by RECIST 1.1. The secondary endpoint for efficacy is progression-free survival. Exploratory endpoints include pharmacokinetics of both ulixertinib and hydroxychloroquine, as well as predictive biomarkers from blood and tumor tissue-based samples. At the time of abstract submission, 26 of the planned 65 patients in Stage 1 had been enrolled. Clinical trial information: NCT05221320. Research Sponsor: BioMed Valley Discoveries, Inc.
Alliance A022102: Randomized phase III trial of mFOLFIRINOX +/- nivolumab vs. FOLFOX +/- nivolumab for first-line treatment of metastatic HER2-negative gastroesophageal adenocarcinoma (GEA).

Haeseong Park, Susan Michelle Geyer, Kelsey Klute, Jonathan Bleeker, Daniel King, Matthew Strickland, Austin Goodrich, Destin Carlisle, Ardaman Shergill, Eileen Mary O’Reilly, Jeffrey A. Meyerhardt, Manish A. Shah; Dana-Farber Cancer Institute, Boston, MA; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; University of Nebraska Medical Center, Omaha, NE; Sanford Health, Sioux Falls, SD; Northwell Health, New Hyde Park, NY; Massachusetts General Hospital, Boston, MA; Alliance Protocol Operations Office, University of Chicago, Chicago, IL; Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY

Background: Platinum/fluoropyrimidine (FP) with PD-1 inhibitor is now established as the standard first-line therapy for most patients with advanced HER2 negative gastric, esophageal, and gastro-esophageal junction (GEJ) adenocarcinoma. The FP doublet chemotherapy backbone, most commonly FOLFOX, is recommended based on marginal survival benefits of taxane-containing triplet therapy at the cost of increased toxicity. Although several agents are approved as standard treatment options in later lines, only about 10% of patients in the US receive a third line of therapy, and very few have the opportunity to benefit from all approved agents in this disease. This challenge will only increase as more agents and targeted therapies are approved. FOLFIRINOX is a triplet regimen commonly used in gastrointestinal malignancies with established safety and often with superior efficacy. Two single arm phase II trials of FOLFIRINOX have reported promising activity in GEA with manageable toxicities. Reported median overall survival (OS) from these trials is around 15 months, which is superior to what is expected from FP doublet first-line chemotherapy (about 11 months). We hypothesize that using upfront triplet therapy with a more effective and less toxic triplet combination will result in improved patient outcomes by optimization of available therapies in GEA. Methods: This study is a randomized phase III, open-label, multicenter clinical trial with the primary objective to determine whether modified FOLFIRINOX (FU 2400 mg/m², leucovorin 400 mg/m², oxaliplatin 85 mg/m², irinotecan 150 mg/m² every 2 weeks) as first-line treatment improves OS compared to mFOLFOX in patients with advanced HER2 negative GEA. Eligible patients will have unresectable or metastatic adenocarcinoma of esophagus, GEJ, or stomach with no prior systemic treatment. Patients must have adequate organ function, and measurable or evaluable disease as defined by RECIST 1.1. Prior neoadjuvant or adjuvant therapy is allowed if completed at least 1 year prior to registration. Patients who will receive nivolumab (mandatory for PD-L1 combined positive score > 5) in addition to chemotherapy must not have any contraindications to immune checkpoint inhibitors. Patients with treated, asymptomatic and stable brain metastases are eligible. The total sample size is 382 evaluable patients for this study (191 patients per arm). The study accrual began January 2023. Clinical trial information: NCT05677490. Research Sponsor: U.S. National Institutes of Health.
A multi-cohort phase I/IIa clinical trial to evaluate the safety, tolerability, and pharmacokinetics of TST001 administered as a monotherapy, with nivolumab or standard of care in patients with locally advanced or metastatic solid tumors: TransStar101.

Yelena Y. Janjigian, Weiijing Sun, Caio Max Sao Pedro Rocha Lima, Satish Shah, Aaron James Scott, Dulabh K. Monga, Madappa N. Kundranda, Amna Falak Sher, Philip Jordan Gold, Jordan Berlin, Manish R. Patel, Olutunji B. Alese, Erika P. Hamilton, Michael Cecchini, Brian Andrew Van Tine, Ben George, Rutika Mehta, Zhenzhong Xia, Caroline Germa, Rashat Y. Gabrail; Memorial Sloan Kettering Cancer Center, New York, NY; University of Kansas Medical Center Department of Internal Medicine, Westwood, KS; NSABP/NGO Oncology and Wake Forest University Baptist Medical Center, Winston-Salem, NC; Gettysburg Cancer Center, Gettysburg, PA; University of Arizona Cancer Center, Tucson, AZ; Allegheny Health Network Cancer Network Institute, Pittsburgh, PA; Banner MD Anderson Cancer Center, Gilbert, AZ; Stony Brook University Hospital, Stony Brook, NY; Swedish Cancer Institute, Seattle, WA; Vanderbilt University Medical Center, Nashville, TN; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; Winship Cancer Institute of Emory University, Atlanta, GA; Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; Yale University School of Medicine, New Haven, CT; Washington University in St. Louis, MO; Medical College of Wisconsin, Milwaukee, WI; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Suzhou Transcenta Therapeutics Co., Ltd., Guangzhou, China; Transcenta Therapeutics, Princeton, NJ; Gabrail Cancer Center, Canton, OH

Background: Gastric cancer (GC) remains the 4th leading cause of cancer death worldwide, accounting for about 7.7% of all cancer related mortality. Despite recent approval of nivolumab in combination with chemotherapy, the median survival of treatment naive Gastric Cancer/gastroesophageal junction cancer (G/GEJ) cancer is only approximately 14 months, even in patients with high CPS PD-L1. Targeting claudin 18.2 (CLDN18.2) in combination with chemotherapy is a clinically validated approach for patients with CLDN18.2 expressing advanced G/GEJ cancer. TST001 is a humanized monoclonal antibody with improved affinity to human CLDN18.2 and enhanced antibody-dependent cellular cytotoxicity (ADCC). In pre-clinical studies, TST001 treatment upregulates PD-L1 expression on CLDN18.2-positive tumor cells. The in vivo analysis showed anti-tumor efficacy of TST001 combined with anti-PD-1 antibody and chemotherapy was superior to combination of anti-PD-1 antibody with chemotherapy or combination of TST001 with chemotherapy. Promising anti-tumor activities have been observed in patients with advanced G/GEJ cancer who have been treated with TST001 alone or in combination with chemotherapy, making the combination of TST001, nivolumab and chemotherapy attractive. Methods: This is a multi-cohort, open-label, multi-center phase I/II first in human (FIH) study of TST001 administered as single agent, in combination with nivolumab or standard of care in the treatment of patients with locally advanced or metastatic solid tumors. Primary endpoints include characterization of TST001 safety profile and the maximum tolerated dose / recommended phase 2 dose. Secondary endpoints include pharmacokinetics, immunogenicity, pharmacodynamics, and efficacy. The study includes two parts. Part A (completed) is a dose escalation of TST001 as a monotherapy. Part B (ongoing) consists of three independent cohorts: cohort A includes combination TST001 + nivolumab+ leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (mFOLFOX6) as 1st line treatment for G/GEJ cancer; cohort B includes TST001 in combination with nivolumab in advanced pre-treated G/GEJ cancer; cohort C includes combination therapy of TST001, gemcitabine, and nanoparticle albumin-bound paclitaxel as 1st line treatment for advanced/metastatic pancreatic cancer. Multiple doses and schedules will be assessed during Part B. Conclusions: Combination of TST001 with nivolumab and chemotherapy has the potential to improve the outcomes of patients with advanced or metastatic CLDN18.2 expressing G/GEJ cancer. Data from this trial will support the selection of the optimal dose and dose regimen of TST001 in these combinations. Enrollment in the trial is ongoing. Clinical trial information: NCT04396821. Research Sponsor: Transcenta Therapeutics Inc.
A randomized, open-label, phase II/III efficacy and safety study of atezolizumab in combination with FLOT versus FLOT alone in patients with gastric cancer and adenocarcinoma of the oesophagogastric junction and high immune responsiveness: The IKF-S633/DANTE trial, a trial of AIO in collaboration with SAKK.

Salah-Eddin Al-Batran, Sylvie Lorenzen, Peter C. Thuss-Patience, Nils Homann, Michael Schenk, Udo Lindig, Vera Heuer, Albrecht Kretzschmar, Eray Goekkurt, Georg Martin Haag, Jorge Riera-Knorrenschild, Claus Bolling, Ralf-Dieter Hofheinz, Stefan Angermeier, Thomas Jens Ettrich, Alexander Reinhard Siebenhuener, Christina Kopp, Claudia Pauligk, Thorsten Oliver Goetze; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, and Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt, Germany; Klinikum rechts der Isar, Technische Universität München, Klinik für Innere Medizin III, München, Germany; Charité–Universitätsmedizin Berlin, Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumormedizinologie, Berlin, Germany; Klinikum Wolfsburg, Med. Klinik II, Wolfsburg, Germany; Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany; Universitätsklinikum Jena, Klinik für Innere Medizin II, Jena, Germany; St. Anna Hospital Herne, Herne, Germany; MVZ Mitte, Onkologische Schwerpunktpraxis, Leipzig, Germany; Hämatologisch-Onkologische Praxis Eppendorf (HOPE) and Universitäres Cancer Center Hamburg (UCCH), Hamburg, Germany; Nationales Centrum für Tumorerkrankungen, Universitätsklinikum Heidelberg, Heidelberg, Germany; Universitätsklinikum Marburg, Klinik für Innere Medizin, Marburg, Germany; Agaplesion Markus Krankenhaus, Hämatologie/Onkologie, Frankfurt, Germany; Universitätsmedizin Mannheim, Tagestherapiezentrum am ITM, Mannheim, Germany; KKH-Kliniken Ludwigshburg, Klinik für Hämatologie und Onkologie, Ludwigshburg, Germany; Universitätsklinikum Ulm, Klinik für Innere Medizin I, Ulm, Germany; Klinik für Hämatologie und Onkologie, Hirslanden Zürich AG, and Swiss Group for Clinical Cancer Research (SAKK), Zürich, Switzerland; Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Frankfurt, Germany; Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt Am Main, Germany

Background: Perioperative FLOT chemotherapy has become a standard of care for locally advanced, resectable esophagogastric adenocarcinoma (EGA). However, patient outcomes are still unsatisfactory. Immune checkpoint inhibitors combined with chemotherapy have proven activity in advanced Her2 negative EGA with PD-L1 expression (KEYNOTE-590, Checkmate-649). Atezolizumab is a PD-L1 inhibitor with established efficacy and tolerability profiles and will be evaluated in this study in the perioperative treatment of potentially resectable EGA in combination with FLOT. As shown at ASCO 2022 for the phase II part of DANTE, adding atezolizumab to FLOT led to improved tumor downsizing and pCR (24% vs 15%). Of note, regression rates further improved with higher PD-L1 expression (33% vs 12% in tumors with CPS ≥10) or in MSI-high tumors (63% vs 27%). Prompted by these results, we decided to transition this trial from the initial phase II to a phase III design. Methods: This is a multinational, prospective, randomized, investigator-initiated, open label phase II/III trial. Patients (pts) with locally advanced, potentially resectable EGA (≥cT2 and/or N-positive) without distant metastases are enrolled. Based on the subgroup analyses of the phase II trial, we decided to limit the future enrollment to pts with high immune responsiveness, i.e. either of the following: MSI-high, PD-L1 CPS≥1, TMB ≥10/MB or EBV+. Eligibility status is centrally evaluated. Pts are randomized 1:1 to 4 pre-operative 2-week cycles (8 weeks) of FLOT (Docetaxel 50 mg/m²; Oxaliplatin 85 mg/m²; Leucovorin 200 mg/m²; 5-FU 2600 mg/m²) plus 840 mg atezolizumab q2w followed by surgery and 4 additional cycles of FLOT/atezolizumab, followed by a total of 8 additional cycles of atezolizumab at 1200 mg every 3 weeks as monotherapy (arm A) or FLOT alone (arm B). Primary endpoint is event-free survival (EFS) as assessed by the Kaplan-Meier-Method. An estimated HR of 0.72 would correspond to a median EFS of 41.67 months for the experimental Arm A. This difference is considered clinically relevant. A total of 556 pts (318 events) will be randomized. As 177/295 pts with PD-L1 positive or MSI status were already enrolled into the phase II portion, additional 379 pts will be enrolled into phase III. Main secondary endpoints are rates of locally assessed pathological regression (complete and nearly complete pathological regression), OS, OS and EFS in the subgroup of pts with PD-L1 CPS ≥5 and ≥10 and pts with MSI, R0 resection, and safety. In addition, a prospective biomarker study including serial circulating tumor DNA analysis before and during treatment will be performed. Recruitment started 2018 and continues for phase III in 2023. Clinical trial information: NCT03421288. Research Sponsor: Roche; Hector Stiftung.
An open-label, multicenter study investigating RP3 oncolytic immunotherapy in combination with first- or second-line systemic atezolizumab and bevacizumab therapy in patients with locally advanced unresectable or metastatic hepatocellular carcinoma.

Tanios S. Bekaii-Saab, Mark Yarchoan, Muneeb Ahmed, David Michael Cohan, Wen Wee Ma; Mayo Clinic, Scottsdale, AZ; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD; Beth Israel Deaconess Medical Center, Boston, MA; Replimune Inc., Woburn, MA; Mayo Clinic, Rochester, MN

Background: Despite advances in treatment for unresectable hepatocellular carcinoma (HCC), long-term survival rates remain poor. The combination of bevacizumab (Bev) and atezolizumab (Atezo) is the preferred frontline therapy for advanced HCC, but a minority of patients (pts) respond, and secondary resistance usually occurs within months. HCC has an immune-suppressed tumor microenvironment, mediated by activated immune checkpoint signaling and angiogenesis pathways, which may contribute to therapeutic resistance. RP3 is a genetically modified herpes simplex virus type 1 (HSV-1) that expresses the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R–), an anti–CTLA-4 antibody-like molecule, CD40 ligand, and 4-1BB ligand. The direct oncolytic effect coupled with immune stimulation by RP3 in the tumor microenvironment is intended to provide systemic antitumor activity and enhance therapeutic response to anti–PD-1/PD-L1 agents, such as Atezo. Preclinical data have demonstrated improved distribution of oncolytic HSV within tumors in combination with Bev, supporting the clinical combination of RP3 with Bev. This study will evaluate the safety and efficacy of RP3 combined with Atezo and Bev as first- (1L) and second-line (2L) systemic therapies for unresectable and advanced HCC.

Methods: The 1L and 2L cohorts will each enroll up to 30 pts. Pts in the 1L cohort may not have received prior systemic treatment; pts in the 2L cohort must have progressed on or following one prior line of systemic therapy, which must have included a PD-1/PD-L1-directed agent. Key inclusion criteria include advanced, unresectable HCC with $\geq 1$ measurable tumor of $\geq 1$ cm in longest diameter, Child-Pugh Class A, and Eastern Cooperative Oncology Group performance status of 0–1. Key exclusion criteria include untreated esophageal and/or gastric varices with bleeding or at high risk for bleeding and macroscopic invasion of tumor into any major blood vessel(s) and/or main bile ducts. Pts with a history of medically refractory hepatic encephalopathy and/or hepatorenal syndrome are also excluded. Pts in the 1L cohort will receive 1200 mg Atezo and 15 mg/kg Bev every 3 weeks (Q3W) together with RP3 intratumorally Q3W for a total of up to 8 doses. Pts in the 2L cohort will receive RP3 every 2 weeks for 4 doses with Bev Q3W starting on cycle (C) 1 day (D) 1, then RP3 and Bev Q3W for up to 4 more doses with Atezo Q3W being added on C4D1. The primary endpoint is overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Secondary endpoints are safety, ORR using HCC modified RECIST, duration of response, complete response rate, and progression-free survival. Clinical trial information: NCT05733598. Research Sponsor: Replimune Inc.
A phase IIa/IIb, open-label trial of BI 907828, an MDM2–p53 antagonist, in patients with locally advanced/metastatic biliary tract carcinoma or pancreatic ductal adenocarcinoma: Brightline-2.

Lipika Goyal, James J. Harding, Makoto Ueno, Angela Lamarca, Teresa Macarulla, Noboru Yamamoto, Joy Hu, Michael Teufel, Angela Maerten, Arndt Vogel, Milind M. Javle; Department of Medicine, Stanford Cancer Center, Palo Alto, CA; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Division of Hepatobiliary and Pancreatic Medical Oncology, Kanagawa Cancer Center, Yokohama, Japan; Fundacion Jimenez Diaz University Hospital, Madrid, Spain; Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology, Barcelona, Spain; Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; Boehringer Ingelheim (People’s Republic of China) Investment Co., Ltd., Shanghai, China; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; Boehringer Ingelheim International GmbH, Ingelheim Am Rhein, Germany; Hannover Medical School, Hannover, Germany; Department of Gastrointestinal Medical Oncology, UT M.D. Anderson Cancer Center, Houston, TX

Background: Biliary tract cancer (BTC) and pancreatic ductal adenocarcinoma (PDAC) carry a median survival of one year in the advanced stages, and effective therapies are urgently needed. Mouse double minute 2 (MDM2) is amplified in ~5–6% of cases of BTC and ~1% of PDAC. MDM2, an E3 ubiquitin ligase, is an endogenous negative regulator of p53. Aberrations affecting MDM2 may drive oncogenesis, and indeed, preclinical as well as emerging clinical data suggest blocking MDM2 in TP53 wild-type tumors may be a potential therapeutic strategy. BI 907828 is an MDM2–p53 antagonist that binds to MDM2 and blocks its interaction with p53, thereby restoring p53 function, leading to cell-cycle arrest and apoptosis in TP53 wild-type tumor cells. In ongoing Phase I studies, BI 907828 has demonstrated initial signs of activity in selected advanced/metastatic solid tumors, including BTC and PDAC. Methods: Brightline-2 is a Phase IIa/IIb, open-label, single-arm, multicenter study (~60 sites) that aims to assess the efficacy, safety, and tolerability of BI 907828 monotherapy in patients with locally advanced, unresectable, or metastatic MDM2-amplified, TP53 wild-type BTC (adenocarcinoma histology; Cohort 1; n=90) or PDAC (Cohort 2; n=10) [NCT05512377]. Cohorts for other solid tumors may be added via protocol amendment. All patients will receive BI 907828 45mg orally every 3 weeks. Key inclusion criteria include: ≥18 years of age; locally advanced/metastatic, histologically confirmed unresectable BTC/PDAC; progression or intolerance to standard therapies; local test indicating MDM2 amplification or MDM2 copy number ≥8 and TP53 wild-type (liquid biopsy not permitted); ≥1 measurable target lesion (RECIST v1.1); and ECOG PS 0/1. A key exclusion criterion is prior treatment with an MDM2–p53 antagonist. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint is objective response rate (ORR; based on blinded central independent review). Secondary endpoints are duration of response, progression-free survival, overall survival, disease control, occurrence of adverse events, and patient-reported health-related quality of life. In Phase IIa, an interim futility analysis will be performed after the initial 30 patients in Cohort 1 have either been followed for ≥12 weeks or have discontinued. If the cohort passes the non-binding interim futility boundary (ORR = 20%), the study will enter Phase IIb, and 60 additional patients will be enrolled onto Cohort 1, totaling 100 patients planned across Cohorts 1 and 2. The final primary analysis will be performed after all treated patients have been followed for ≥12 weeks or until study discontinuation. As of 13 December 2022, 1 patient has been enrolled. Clinical trial information: NCT05512377. Research Sponsor: Boehringer Ingelheim.
Randomized phase 2 study of maintenance olaparib vs olaparib plus durvalumab for DNA damage repair (DDR) gene mutated unresectable or metastatic biliary tract cancer (BTC) with durable response to first-line platinum-based chemotherapy: OPTIMUM trial.

YunJung Kim, Boram Ok, Inkeun Park, Baek-Yeol Ryoo, Kyu-Pyo Kim, Changhoon Yoo; Clinical Trial Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: BTC is rare and aggressive disease with heterogeneous genetic profiles. Gemcitabine plus cisplatin (GemCis) with or without durvalumab is the standard first-line therapy but further improvement in survival outcomes is needed. In a prior study (Chae HJ et al, Eur J Cancer 2019), germline or somatic mutations in DDR genes including BRCA are detected more than half of BTC patients and associated with better survival outcomes with platinum-based chemotherapy. As the potential efficacy of Olaparib in DDR-mutated cancers and synergism between PARP inhibitors and immune checkpoint inhibitors, we designed randomized phase 2 trial investigating the efficacy and safety of olaparib monotherapy vs olaparib plus durvalumab in BTC patients as maintenance therapy for BTC patients who showed durable response to first-line platinum-based chemotherapy. Methods: This is a randomized, open-label phase 2 study conducted in a single center (Asan Medical Center, Seoul, Korea). Key eligibility criteria include histologically documented locally advanced unresectable or metastatic BTC, no progression at least 16 weeks with first-line platinum-based chemotherapy, DDR mutations on targeted sequencing of tumor tissues and ctDNA, ECOG performance status 0–1, and adequate organ function. Eligible patients will be randomized 1:1 into olaparib monotherapy arm (300 mg twice daily, every 4 weeks) or olaparib plus durvalumab (1,500 mg intravenous, every 4 weeks) arm. Study treatment is continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. Response evaluation is performed every 8 weeks (fixed). Stratification factors are tumor location (intrahepatic vs extrahepatic/gallbladder) and best response to platinum-based chemotherapy (CR/PR vs SD). The six-month progression-free survival rates are the primary endpoint and overall survival, progression-free survival, response rates, and safety profiles are secondary endpoints. A total of 62 patients (31 for each arm) are planned, and 23 (37%) patients (ATM [n=6], BRCA2 [n=7], CHEK2 [n=2], BRCA1 [n=1], RAD51C [n=1], and PBRM1 [n=1]) are enrolled as of Jan 2023. Clinical trial information: NCT05222971. Research Sponsor: AstraZeneca Korea Ltd.
Autologous cytotoxic T-cell receptor T cell therapy (SCG101) against hepatitis B surface antigen phase I/II trial for patients with advanced hepatitis B-related hepatocellular carcinoma.

Ghassan K. Abou-Alfa, Wei-Peng Yong, Stephen Lam Chang, Jia Fan, Han Chong Toh, Thomas Yau, SuPin Choo, Jing Wang, Nicole Kusuma, Christy Ma, Shukui Qin; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, Cornell University, New York, NY; National University Hospital, Singapore, Singapore; Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China; Liver Cancer Institute, Zhongshan Hospital, and Key Laboratory of Carcinogenesis and Cancer Invasion (Ministry of Education), Fudan University, Shanghai, China; National Cancer Center of Singapore, Singapore; Queen Mary Hospital, Hong Kong, China; Curie Oncology, Singapore, Singapore; SCG Cell Therapy Pte Ltd, Shanghai, China; SCG Cell Therapy, Singapore, Singapore; SCG Cell Therapy Pte Ltd, Singapore, Singapore; Nanjing Tianyishan Hospital, Nanjing, China

Background: The overall prognosis of patients with advanced Hepatitis B-related hepatocellular carcinoma (HCC) remains poor, and treatment options are limited. In an IIT study conducted in China (NCT05339321), SCG101 following lymphodepletion (cy-flu) as second-line setting or beyond in patients with Hep B-related HCC has shown acceptable safety profile, reduction in HBsAg levels (>1 log) and tumor control. A phase I/II trial has been initiated to evaluate safety and RP2D of autologous SCG101 T cell therapy in Hepatitis B virus-related HCC (NCT05417932). Methods: This multicenter, open-label, 3+3 dose-escalation phase I trial is ongoing across 7 sites in the United States, Singapore and Hong Kong SAR, and a parallel study is done in mainland China across 8 sites. Eligible patients have a histologically confirmed HCC, not amenable to curative intent (surgery or locoregional therapy) and failed ≥2 standard line of therapies, match any of HLA-A*02:01, *02:02, *02:03, *02:04, *02:07, *02:09, *02:16, have positive serum (or tumor) HBsAg, HBV-DNA <2000 IU/ml, BCLC B or C, CP≤7, with measurable disease at screening (mRECIST and RECIST v1.1), ECOG PS<1. Patients with CNS metastasis, prior liver transplant, autoimmune disease or prior cell therapy are excluded. SCG101 T cells is manufactured in Singapore under cGMP and ship to all study sites across the U.S, Singapore and Hong Kong SAR, while SCG101 T cells for the China sites is manufactured in SCG Cell Therapy's China facility. Patients will receive a single dose of SCG101 T cell therapy following lymphodepletion (cy-flu). Endpoints include safety, MTD and RP2D. Secondary endpoints include ORR, DOR, PFS, OS, changes in serum HBsAg. Safety is monitored together with Data Review Committee. The study is actively enrolling, and the phase II portion of the trial is expected to be initiated by H2 2023. Autologous SCG101 T cell therapy may provide a new treatment option for patients with advanced Hepatitis B virus-related HCC. Clinical trial information: NCT05417932. Research Sponsor: SCG Cell Therapy Pte Ltd.
ABC-12: Exploring the microbiome in patients (pts) with advanced biliary tract cancer (BTC) in a first-line study of durvalumab in combination with cisplatin/gemcitabine (cis/gem).

Mairead Geraldine McNamara, Hayley Timmins, Ashley Osborne, Rebecca Cox, Harpreet Singh Wasan, Pipa Corrie, Roopinder Gillmore, Shivan Sivakumar, Yuk Ting Ma, Olusola Olusesan Faluyi, Arvind Arora, Seema Arif, Jo Canham, Chris Hurt, Richard Hubner, John A Bridgewater, Richard Adams, Juan W. Valle; University of Manchester/The Christie NHS Foundation Trust, Manchester, United Kingdom; Cardiff University, Cardiff, United Kingdom; The Christie, Manchester, United Kingdom; Hammersmith Hospital Imperial College, London, United Kingdom; Addenbrooke’s Hospital, Cambridge, United Kingdom; Royal Free, London, United Kingdom; University of Oxford, Oxford, United Kingdom; University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; Clatterbridge Cancer Centre, Wirral, United Kingdom; University Hospital of Nottingham NHS Trust; University of Nottingham, Nottingham, United Kingdom; Velindre Cancer Centre, Cardiff, Cardiff, United Kingdom; Centre for Trials Research, Cardiff University, Cardiff, United Kingdom; Medical Oncology Department, The Christie NHS Foundation Trust, Manchester, UK, Manchester, United Kingdom; UCL Cancer Institute, London, United Kingdom

Background: Durvalumab/cis/gem improved overall survival (OS) in pts with advanced BTC versus placebo/cis/gem (Oh et al. NEJM Evid 2022). Disruption of the microbiota may impair tumour response to immunotherapy and chemotherapy and a better understanding of its role in the efficacy of these therapeutics in advanced BTC is required. Methods: This is a multi-centre, single arm trial exploring the microbiome in pts receiving durvalumab 1500 mg intravenously (IV) Q3w, in combination with cis 25 mg/m², gem 1000 mg/m² (Days 1 and 8, Q3w) up to 8 cycles, followed by durvalumab 1500 mg as monotherapy Q4w, until progression or intolerable toxicity. Pts with an ECOG performance status of ≤1 and histologically-proven BTC, including cholangiocarcinoma and gallbladder carcinoma, who have had no prior systemic chemotherapy for locally advanced or metastatic disease are eligible. Pts must provide a saliva and stool sample prior to commencement of durvalumab/cis/gem and at 18 weeks, or at progression (if earlier than 18 weeks). Taxonomic profiling via 16S Ribosomal ribonucleic acid gene sequencing will examine the differences in the diversity and composition of the pt gut microbiome. Pts must also have availability of a tumour biopsy. This study plans to recruit 70 pts from 10 UK centres (over 12 months). The primary objective is to determine the difference in baseline alpha diversity between “responders” (partial or complete response) and “non-responders” at 18 weeks (RECIST 1.1) in patients treated with durvalumab/cis/gem. Secondary objectives include investigation of the association between microbiome parameters and objective response rate, tumour control (partial + complete response + stable disease), progression-free and OS, and to investigate the interaction between treatment effect and microbiome parameters on clinical outcomes. The tumour biopsy will be used for research into the tumour microbiome and/or factors that may influence response to chemotherapy/immunotherapy, including, but not limited to tumour mutation burden, programmed cell death 1/programmed death-ligand 1 status, and microsatellite instability status. Clinical trial information: ISRCTN11210442. Research Sponsor: Astra Zeneca.
Phase II trial of XmAb20717 (vudalimab) in patients with advanced biliary tract cancers.

William Joseph Chapin, Parul Agarwal, Lisa DiCicco, Rayleigh Palmer, Nadia Cenou, Alexander Chan Chi Huang, Thomas Benjamin Karasic; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA

Background: For patients with advanced biliary tract cancers (BTCs), gemcitabine and cisplatin has been the standard-of-care first-line therapy, with a median overall survival (OS) of 11.7 months. More recently, TOPAZ-1 demonstrated a modest, but significant overall survival benefit (HR 0.80; 95% CI 0.66 – 0.97) to the addition of durvalumab to gemcitabine and cisplatin with a median OS of 12.8 months. However, for patients without targetable molecular variants, second-line and beyond options are limited, with FOLFOX demonstrating an overall response rate (ORR) of 5% and increase in median overall survival by 0.9 months compared to active symptom control. In patients with advanced BTCs, combination immunotherapy approaches with PD-1 or PD-L1 plus CTLA-4 inhibitors have been associated with improved ORRs of 10.8% - 23% compared to ORRs of 3 – 7% observed with single agent PD-1 or PD-L1 inhibitors. XmAb20717 (vudalimab) is a novel, bispecific antibody targeting PD-1 and CTLA-4 which demonstrated an ORR of 14.1% in a phase I dose expansion cohort of patients with advanced malignancies, including patients that had experienced disease progression on prior immune checkpoint inhibitors. Methods: We initiated a single-arm, phase II clinical trial with a Simon two-stage mini-max design to evaluate the efficacy of XmAb20717, in terms of ORR, in patients with advanced biliary tract cancers previously treated with gemcitabine-based chemotherapy. In the first stage, 13 patients evaluable for efficacy will be accrued. If no responses are observed in these 13 patients, the study will be stopped for futility. Otherwise, 14 additional patients evaluable for efficacy will be accrued to total 27 evaluable patients. If 4 or more responses are observed in these 27 patients, then the null hypothesis will be rejected. XmAb20717 (10 mg/kg) is administered intravenously on days 1 and 15 of a 28-day cycle. Important inclusion criteria include that patients with FGFR2 fusions, NTRK fusions, or IDH1 mutations must have received molecularly targeted therapy unless contraindicated or refused. Patients are not eligible if they have received prior immune checkpoint inhibitor therapy. Correlative studies will include longitudinal peripheral blood collection for circulating immune cell profiling. As of January, 2023, 8 patients have been enrolled with enrollment ongoing. Clinical trial information: NCT05297903. Research Sponsor: Xencor.
Phase II study on safety and efficacy of NMS-01940153E, an MPS1 inhibitor with first-in-class potential, in adult patients with unresectable hepatocellular carcinoma (HCC) previously treated with systemic therapy.

Lorenza Rimassa, Maria Reig, Silvia Damian, Domenico Roberti, Sara Maruzzelli, Fabio Gasparri, Pamela Ghioni, Maria Teresa De Pietro, Tiziana Pressiani, Marco Sanduzzi Zamparelli, Matteo Duca, Alessia Montagnoli, Arturo Galvani, Elena Ardini, Antonella Isacchi, Cristina Davite, Patrizia Crivori, Lisa Mahnke; Humanitas University, Department of Biomedical Sciences; IRCCS Humanitas Research Hospital, Medical Oncology and Hematology Unit, Rozzano, Italy; Hospital Clinic Barcelona, Liver Oncology Unit; BCLC group, FUNDACIO/IDIBAPS; CIBEREHD; Universitat de Barcelona, Barcelona, Spain; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; University of Campania, Naples, Italy; Nerviano Medical Sciences S.r.l., Global Clinical Development, Nerviano (MI), Italy; Nerviano Medical Sciences S.r.l., Discovery Pharmacology, Nerviano (MI), Italy; IRCCS Humanitas Research Center, Rozzano, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Nerviano Medical Sciences S.r.l., Global Asset Leadership, Nerviano (MI), Italy; Nerviano Medical Sciences S.r.l., Oncology - Discovery, Nerviano (MI), Italy; Nerviano Medical Sciences Inc., Boston, MA

Background: Monopolar Spindle 1 (MPS1) kinase regulates the spindle assembly checkpoint (SAC) which ensures proper division of chromosomes during mitosis. MPS1 is overexpressed in several tumors, including hepatocellular carcinoma (HCC), where it correlates with tumor features and poor overall and disease-free survival. NMS-01940153E is a novel, highly potent and selective small molecule inhibitor of MPS1 kinase with long residence time and strong preclinical anti-tumor activity in different tumor types. In HCC lines, specifically, NMS-01940153E showed ~2-Log higher anti-proliferative activity compared to sorafenib, lenvatinib, and regorafenib. In a previous open-label first-in-human (FIH) study, CL1-81694-001 (EudraCT 2014-002023-10), signs of activity in HCC were detected. Recently, the treatment paradigm for advanced HCC has changed, with immunotherapy combinations in first line and TKIs shifted in later lines. However, the overall prognosis of patients with advanced HCC remains poor, and there is a strong need of new drugs in this setting. NMS-01940153E novel mechanism of action, inhibiting the SAC and interfering with genomic stability in HCC, may offer a new therapeutic option in HCC. Based on the promising FIH results, a Phase I/II study, MPSA-153-001 (EudraCT 2020-001002-26), was initiated in patients with HCC previously treated with more than one systemic therapy. Methods: The Phase II part of the MPSA-293-001 trial is designed as a two-stage study with an interim analysis for futility and safety rules for unacceptable toxicity. The primary objective is to assess the antitumor activity of NMS-01940153E in adult patients with unresectable HCC previously treated with systemic therapy measured as objective response rate (ORR) by investigator-assessed RECIST 1.1. Secondary endpoints are safety, PK, ORR as measured by investigator-assessed mRECIST, DoR, PFS and OS. Exploratory endpoints include biomarkers. NMS-01940153E is administered IV, on days 1, 8 and 15 every 4 weeks at the RP2D of 100 mg/m2/wk, which showed PK in a predicted active range. Key eligibility criteria are 1) diagnosis of HCC; 2) disease progression on standard-of-care treatment including an immune checkpoint inhibitor as first line and at least one TKI; 3) no more than 3 prior systemic treatment lines. Interim evaluation for futility will be undertaken as soon as the first 10 evaluable patients will be enrolled. If at least 1 responder is observed with no safety issues, enrollment will proceed up to 38 evaluable patients. Otherwise, the study will be terminated for futility. An independent DSMB will review the interim results and provide recommendation on the study progress. Recruitment is currently ongoing in Italy and Spain and an FDA “Study May Proceed Notification” was received in January 2023. Clinical trial information: NCT05630937. Research Sponsor: Nerviano Medical Sciences S.r.l.
NeoTACE: A multicenter, randomized study evaluating the efficacy and safety of neoadjuvant HAIC for TACE plus donafenib in BCLC B stage hepatocellular carcinoma outside of up-to-seven.

Xiaodong Wang; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Interventional Therapy, Peking University Cancer Hospital & Institute, Beijing, China

Background: Transarterial chemoembolization (TACE) is standard treatment for hepatocellular carcinoma (HCC) patients in BCLC B stage, while a number of studies demonstrated compromised effect of TACE for patients with large HCC or tumor burden outside of up-to-7. Recently, two phase 3 studies showed the survival benefit of Hepatic arterial infusion chemotherapy (HAIC) for large HCC and as neoadjuvant treatment for HCC outside of Milan criteria. A Phase 3 study also showed the survival benefit of donafenib for unresectable HCC compared with sorafenib. Here, we propose a prospective randomized study to investigate the benefit of HAIC as a neoadjuvant therapy for TACE plus donafenib in unresectable BCLC B stage HCC outside of up-to seven. Methods: This is a multicenter, open-label, randomized study designed to evaluate the efficacy and safety of neoadjuvant HAIC for TACE plus donafenib compared with TACE plus donafenib in BCLC B stage unresectable HCC outside of up-to-seven. Participants are randomized in 1:1 ratio to either Arm A, receiving 2-4 cycles neoadjuvant HAIC treatment plus donafenib initially, then TACE plus donafenib sequentially, or Arm B, just receiving TACE treatment plus donafenib. HAIC consisted of infusions of oxaliplatin (35 mg/m2 for 2 hours), followed by 5-fluorouracil (600 mg/m2 for 22 hours) on day1-3 every 4 weeks. The primary endpoint is PFS, and the secondary endpoints are OS, ORR, DCR, and adverse events. We hypothesize that neoadjuvant HAIC for TACE plus donafenib will improve PFS from 6 months to 11 months, with the hazard ratio of 0.55. With one-sided significance level of 0.05 and power of 0.8, the sample size for randomization will be 156. The study, registered with clinical trial ID of NCT05171166, started enrolment in Feb 2022. As of Oct 2022, 65 patients have been enrolled and 11 patients have been randomized. Clinical trial information: NCT05171166. Research Sponsor: Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (No. ZYLX202117).
ADJUBIL: A phase II study of immunotherapy with durvalumab and tremelimumab in combination with capecitabine or without capecitabine in adjuvant situation for biliary tract cancer.

Thorsten Oliver Goetze, Lisa Kochen, Doerthe Vortmeyer, Salah-Eddin Al-Batran, Timorshah Habibzada, Marius Brunner, Thomas Jens Ettrich, Maria A Gonzalez-Carmona, Claus-Henning Kohne, Dominik Paul Modest; Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt Am Main, Germany; Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany; Krankenhaus Nordwest, University Cancer Center Frankfurt, Frankfurt, Germany; Uniklinik Göttingen, Göttingen, Germany; Universitätsklinikum Ulm, Klinik für Innere Medizin I, Ulm, Germany; Bonn University Hospital, Bonn, Germany; Department of Gynaekologie, Oldenburger Frauenklinik, Oldenburg, Germany; Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universitaet Berlin and Humboldt-Universitaet Zu Berlin, Department of Hematology, Oncology, and Cancer Immunology (CVK), Berlin, Germany

Background: Despite improvements in multidisciplinary management, patients with biliary tract cancer (BTC) have a poor outcome. Only 20% of patients are eligible for surgical resection with curative intent, with 5-year overall survival of less than 10% for all patients. Data regarding pure adjuvant chemotherapy in BTC’s are conflicting and the SOC of the western world is currently capecitabine according to the British BILCAP- trial, even though BILCAP was formally negative. Based on the positive data for durvalumab in the TOPAZ-1 – trial in BTC and for STRIDE- regimen in HCC according to the Himalaya-data, evaluation of IO- combination in the adjuvant setting seems to be promising. Preclinical studies indicate that the antibody combination results in stronger and more durable anti-tumor effects than single therapies by synergistically modulating the immunosuppressive tumor microenvironment which is particularly rich in cholangiocarcinoma. The aim of this study is the assessment of the clinical activity of the anti-PD-L1 (programmed-death 1-ligand) antibody durvalumab and the anti-CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) antibody tremelimumab in combination with or without capecitabine in patients with respectable BTC in the adjuvant situation. This is a randomized phase II study as a proof-of-concept for a potentially larger research program. Methods: The ADJUBIL trial is an open-label, multicenter phase II study, including patients with BTC after curative surgery with no previous systemic treatment. Patients are randomly assigned to receive tremelimumab (300mg, one dose) plus durvalumab (1500mg every 4 weeks; STRIDE, for a maximum of 12 months), with or without capecitabine (for 8 cycles). Forty evaluable patients will be enrolled in the study (1:1) to receive anticancer treatment until disease recurrence or intolerable toxicities. Primary objective is to assess the anti-tumor activity of the treatment in both arms by the recurrence-free survival rate after 12 months (RFS@12). Secondary endpoints are recurrence-free survival, overall survival, toxicity, and quality of life. Exploratory endpoints: Explore predictive biomarkers for recurrence-free survival and overall survival. Study start of the ADJUBIL trial was in June 2021. By January 2023, 12 centers across Germany have been initiated and a total of 8 out of 40 planned patients (1:1) have been enrolled. The study is currently ongoing. Clinical trial information: EUCTR2021-002389-41. Research Sponsor: AstraZeneca.
Durvalumab and tremelimumab for hepatocellular carcinoma in patients listed for a liver transplant.

Davendra Sohal, Khaled Fahmy Abouelezz, Katie Moreland, Ralph Quillin, Kristina Lemon, Adam Rojan, Olugbenga Olanrele Olowokure, Ali Kord, Shimul Shah; University of Cincinnati, Cincinnati, OH; University of Cincinnati Medical Center, Cincinnati, OH; University of Cincinnati College of Medicine, Cincinnati, OH; University Of Cincinnati, Cincinnati, OH

Background: Hepatocellular carcinoma (HCC) is an aggressive malignancy, developing most often in the setting of liver cirrhosis (Sohal et al Current Oncol Rep 2011; Gordan et al JCO 2020). For advanced disease, immunotherapy has now become standard of care – a combination of atezolizumab and bevacizumab has shown the best overall survival outcome so far (Finn et al NEJM 2020). For earlier stage disease, however, there is no systemic therapy standard. The best treatment for HCC in the setting of cirrhosis is a liver transplant allowing potential cure for both the cancer and cirrhosis. Nonetheless, 25-35% of patients fail to reach liver transplant because of disease progression while waiting for a transplant (Sinha et al, Hepatology 2019) and approximately 15% experience HCC recurrence after transplant (Mehta et al, Transplantation 2020). Taken together, this constitutes a large subset of this patient population who cannot achieve a cure. Given the success of immunotherapy in the advanced setting, it is imperative to study this in the pre-transplant setting, to improve the outcomes cited above. However, there is a theoretical risk of graft rejection with immunostimulatory treatment. Methods: This is a single-arm, open-label, Phase II, multicenter study designed to evaluate the safety and efficacy of durvalumab and tremelimumab for the treatment of HCC patients who have cirrhosis or portal hypertension and are eligible for listing for a liver transplant. Eligibility requirements include adult patients with HCC within UCSF criteria, a Child-Pugh score of up to 7, and ECOG PS of 0 or 1. Treatment includes an immunotherapy combination of 1 dose of tremelimumab and 5 doses of durvalumab for up to 4 months. After a minimum 28-day gap following the final durvalumab dose, patients undergo locoregional therapy per institutional standards. After a minimum 72-day gap from the end of immunotherapy, patients undergo liver transplant. Primary outcome is a binary endpoint, and it will be assessed in patients undergoing liver transplant. Historically, 10-20% of patients are expected to experience acute cellular rejection within 30 days of transplant. We propose that an observed proportion of 20% treatment failure will be a clear indicator of safety in this pilot study, whereas an observed proportion of 50% failure will be a clear indicator of failure. Using these guardrails, with at least 20 patients going to transplant, we will have 80.6% power to demonstrate a failure proportion of 20% (4 patients experiencing failure) versus a null of 50% (10 patients experiencing failure), with a one-sided alpha of 0.05. With 25 patients going to transplant, the power will increase to 86% (other parameters being the same). Clinical trial information: NCT05027425. Research Sponsor: AstraZeneca.
An open-label window of opportunity trial to evaluate the activity of durvalumab and tremelimumab with platinum-based chemotherapy (gemcitabine and cisplatin) in intrahepatic cholangiocarcinoma.

Olumide B. Gbolahan, Mehmet Akce, Darryl Alan Outlaw, Grant Richard Williams, Sushanth Reddy, Jason Denbo, Richard D. Kim, Bassel F. El-Rayes, J. Bart Rose; Emory University School of Medicine, Atlanta, GA; Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL, Birmingham, AL; University of Alabama at Birmingham, Birmingham, AL; Department of Surgical Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The University of Alabama at Birmingham, Birmingham, AL

Background: Following surgical resection, the rate of recurrence of intrahepatic cholangiocarcinoma (ICC) is high. Expert groups recommend preoperative systemic therapy, particularly for resectable ICC with features that portend a high risk of recurrence. Based on data from ABC-02 the combination of gemcitabine and cisplatin (GC) is often used. This provides an objective response rate (ORR) of only 20% in ICC. The addition of durvalumab, an anti-PDL1 inhibitor to GC improves overall survival (OS) in the metastatic setting and is associated with an ORR of about 30%. On the other hand, while the addition of nab-Paclitaxel to GC provides an ORR of 34%, it was not associated with an improvement in OS in biliary tract cancer. It is therefore rationale to continue to explore and optimize immune checkpoint inhibitor development in ICC. We designed this study to determine the activity of durvalumab (D) and tremelimumab (T) (anti-CTLA4 ICPI) in combination with GC in resectable ICC with high-risk features. We plan to explore tumor intrinsic and tumor microenvironment related factors that will be associated with response (or lack thereof) to ICPI. Methods: This is a multicenter open-label, window of opportunity trial of the combination durvalumab and tremelimumab in combination with GC in resectable ICC with high-risk features. Inclusion criteria includes patients ≥18years with radiologically measurable and biopsy proven ICC that is surgically resectable but with high risk features (based on multidisciplinary tumor board discussion). Prespecified high-risk features include tumor size >5cm, T1b-T4 lesion, multifocal tumors/tumor with satellite lesions, suspicious or involved lymph nodes (N1) and vascular involvement all thought to be technically resectable. Patients with extrahepatic metastasis will be excluded. D will be administered at 1500mg IV on Day 1 every 3 weeks for up to a maximum of 4 cycles. T, 300mg will be administered on Day 1 of cycle 1 only. G (1000mg/m2) and C (25mg/m2) will be administered by IV infusion on Days 1 and 8 every 3 weeks for a maximum of 4 cycles. The primary outcome measure is to demonstrate an ORR of 52%. Secondary objectives are to assess the feasibility and safety of the combination in ICC. Given the historical objective response rate of 25% and using one-sided exact test for single proportion, we will have 80% power to reject 25% ORR at α=0.05 when we observe ORR of 52% (Ho: Po=0.25 vs. Ha: Pa=0.52) from the study sample. The study is open at the O’Neal Comprehensive Cancer Center at the University of Alabama and will be open at other centers in the next few months. Clinical trial information: NCT04989218. Research Sponsor: AstraZeneca.

Sherise C. Rogers, Ilyas Sahin, Jesus C. Fabregas, Ibrahim Nassour, Brian Hemendra Ramnaraign, Kathryn Hitchcock, Steven J. Hughes, Ji-Hyun Lee, Omar Roger Kayaleh, Anita Ahmed Turk, Z. Hugh Fan, Karen Bullock Russell, David L. DeRemer, Carmen Joseph Allegre, Thomas J. George; University of Florida/UF Health Cancer Center, Gainesville, FL; University of Florida Health Cancer Center, Gainesville, FL; Orlando Health, Orlando, FL; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; University of Florida, Gainesville, FL; Tallahassee Memorial HealthCare, Tallahassee, FL

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 neoadjuvantly. Liposomal irinotecan injection (Nal-IRI) 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 multidisciplinary GI tumor board (resectable vs. borderline), adequate cardiac, renal, hepatic function and ECOG performance status of 0 to 1. Pts receive NEO-N-IRI regimen as per 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 perioperative 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. Enrollment continues to a maximum of 28 evaluable pts to demonstrate a reduction in historical 30-day postoperative complication rate. Microbiota specimens will be collected for exploratory analysis. Clinical trial information: NCT03483038. Research Sponsor: Ipsen; UF Health Cancer Center.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route/Duration</th>
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<tbody>
<tr>
<td>Nal-IRI</td>
<td>50 mg/m²</td>
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<tr>
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<td>Leucovorin</td>
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<tr>
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Alliance A021804: A prospective, multi-institutional phase II trial evaluating temozolomide versus temozolomide and olaparib for advanced pheochromocytoma and paraganglioma.

Jaydira Del Rivero, Kimberly Perez, Susan Michelle Geyer, Maged F. Khalil, Aishwarya Vijendran, Andrea Kordaris-Corkill, Ardaman Shergill, Kristen Renee Spencer, Heloisa P. Soares, Charles D. Lopez, Andrew B. Nixon, Amylou C. Dueck, Jeffrey A. Meyerhardt, Eileen Mary O’Reilly; National Cancer Institute/National Institutes of Health, Bethesda, MD; Dana-Farber Cancer Institute, Boston, MA; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; Lehigh Valley Health Network, Allentown, PA; University of Chicago, Chicago, IL; Mayo Clinic, Rochester, MN; Department of Medicine, Section of Hematology & Oncology, University of Chicago Medical Center, Chicago, IL; NYU Perlmutter Cancer Center, NYU Langone Health, New York, NY; Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT; Oregon Health & Science University, Portland, OR; Duke University Medical Center, Durham, NC; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine tumors (NETs) that arise from chromaffin cells. Few antitumor therapies have been developed for patients (pts) with advanced PHEO/PGLs (APP). Potent poly (ADP-ribose) polymerase (PARP) is activated after DNA damage and regulates base excision repair, homologous recombination and non-homologous end joining. Inhibition of PARP enzymatic activity blocks PARP-mediated DNA repair, therefore PARP inhibitors can be directly cytotoxic to tumor cells which then permits synergy with agents that increase prevalence of single-strand breaks in tumor models. Temozolomide (TMZ) is an alkylating agent that induces single-strand DNA breaks and therefore is an optimal therapeutic pair with a PARP inhibitor. We are conducting a phase II multi-institutional study to evaluate the antitumor activity of TMZ and olaparib (OLA (a PARP inhibitor)) in patients with APP. Methods: Patients with APP with radiographic evidence of disease progression by RECIST v1.1 in the 12 months prior to registration can be enrolled in this phase II randomized study. Patients will be randomized in a 2:1 allocation with more patients to Arm 1. Arm 1 will receive TMZ 75 mg/m2 daily and OLA 200 mg twice daily on days 1-7 of a 21-day cycle. Arm 2 will receive TMZ 200 mg/m2 daily on days 1-5 of a 28-day cycle. Treatment on Arm 1 will continue for 13 cycles, followed by OLA maintenance until disease progression. Treatment on Arm 2 will continue for 13 cycles or until disease progression. The primary objective is to compare the progression-free survival between the two arms with a planned interim analysis for futility. Secondary endpoints include safety, response rate, and overall survival. Correlative endpoints include biochemical response and biomolecular markers (germline succinyl dehydrogenase mutations and tumor status of the repair enzyme methylguanine-DNA methyltransferase). We anticipate a null PFS median of approximately 5.4 months. We plan to accrue a total of 76 patients (randomized at a rate of 2:1 with more patients enrolled to the TMZ+OLA arm) in 38 months with a minimum follow-up of 2.5 months to achieve 56 PFS events. This design includes one interim analysis for futility using Rho Family spending functions (Rho = 2.5) and will yield 89% power to detect a hazard ratio (HR) of 0.5 (median PFS of 5.4 vs. 10.8 months) assuming exponential survival and using a one-sided log-rank test with type I error rate of 0.11. Clinical trial information: NCT04394858. Research Sponsor: U.S. National Institutes of Health.
LANTana trial protocol: An open label, single arm, phase Ib study to evaluate the effect of pre-treatment with ASTX727 (a demethylating agent) followed by lutetium Lu 177 dotatate in patients with progressive, metastatic neuroendocrine neoplasias (NENs).

Rohini Sharma, Caroline Ward, Mitesh Naik, Saraih Khan, Tara Barwick, Maria Martinez, Hooshang Izadi, Eric O. Aboagye; Imperial College London, London, United Kingdom; Imperial College Healthcare NHS Trust, London, United Kingdom; Oxfordbrookes University, London, United Kingdom

Background: Neuroendocrine neoplasias (NENs) are characterised by the presence of somatostatin receptors (SSTR) on cell surface, in particular SSTR2. Somatostatin and its stable analogue (SSA) bind with high affinity to SSTR2. SSA can be radiolabelled, to both stage NENs using positron emission tomography (PET), and to deliver selective radiotherapy; peptide receptor radionuclide therapy (PRRT). PRRT consists of SSA linked to the long acting radionuclide. Radiolabelled SSA binds to SSTR2 and the complex is internalised delivering high dose radiation directly to the cancer. PRRT has been significantly improve survival outcomes and maintain quality of life in metastatic disease. Suitability for PRRT depends on presence of SSTR2 as determined by PET imaging, commonly with [68Ga]-dotatate-PET. 20% of patients will have low or no uptake on [68Ga]-dotatate-PET precluding PRRT. The upstream promoter region of SSRT2 is methylated, with percentage of methylation correlating with SSTR2 expression. We have shown that the use of the demethylating agent, guadecitabine, increases uptake on PET imaging in such that tumours previously negative on PET imaging, become positive, correlating with a dose dependent increase in tumoural SSTR2 expression. Combination guadecitabine and PRRT was well tolerated in vivo models of NETs. Overall aim was to utilise [68Ga]-dotatate-PET as a biomarker of SSTR2 re-expression following treatment with the demethylating agent, ASTX727, such that patients previously unsuitable for PRRT can receive therapy, improving clinical outcome. 1) Utilise [68Ga]-dotatate-PET to image epigenetic regulation of SSTR2 in response to ASTX727. 2) Evaluate clinical efficacy and safety of ASTX727 pre-treatment in combination with PRRT. 3) Explore impact on quality of life of combination therapy. Methods: 27 patients with no or equivocal uptake on [68Ga]-dotatate-PET will be enrolled. [68Ga]-dotatate-PET will be performed at baseline and after 8days of ASTX727 (oral, fixed dose 100mg cedazuridine + 35mg decitabine). If there is a significant increase in PET uptake, patients will receive combination ASTX727 and PRRT (Lutathera). Treatment will be repeated every 2months for 4 cycles. Response assessment (RECIST 1.1), tolerability and QoL will be assessed at start of each cycle. Tumour biopsies will be taken at baseline, and after cycle1 of ASTX727 (n=5), for SSTR2 methylation. Methylation will be correlated with PET uptake and outcome. LINE-1 methylation in peripheral blood monocytes will be assessed throughout. Current enrolment: 4. Clinical trial information: NCT05178693. Research Sponsor: AAA.
Open-label, single arm phase II trial investigating the efficacy, safety and quality of life of neoadjuvant chemotherapy with liposomal irinotecan combined with oxaliplatin and 5-fluorouracil/folinic acid followed by curative surgical resection in patients with hepatic oligometastatic adenocarcinoma of the pancreas (HOLIPANC).

Florian Gebauer, Thomas Schmidt, Alexander Damanakis, Alexander Quaas, Duygu Cay, Linde Kehmann, Burkhardt Deuß, Swantje Held, Jens Werner, Alexander Rehders, Christian Schineis, Daniel Reim, Uwe A Wittel, Jens Werner, Tim Glowka, Ulrich Ronellenfitsch, Georg Wittberger, Sören T Mees, Christiane J. Bruns, Dirk Waldschmidt; University Cologne, Cologne, Germany; University of Cologne, Cologne, Germany; Servier Deutschland GmbH, München, Germany; Clinasses Inc, Leverkusen, Germany; Clinasses Inc., Leverkusen, Germany; University of Regensburg, Regensburg, Germany; University of Dusseldorf, Dusseldorf, Germany; University of Berlin - Charité, Berlin, Germany; Klinik und Poliklinik für Chirurgie, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; General and Visceral Surgery, University Medical Center Freiburg, Freiburg, Germany; University of Munich, Munich, Germany; University of Bonn, Bonn, Germany; University of Halle, Halle (Saale), Germany; University of Aachen, Aachen, Germany; Klinikum Dresden, Dresden, Germany

Background: As of today, the recommendation for patients with adenocarcinoma of the pancreas and hepatic metastases is systemic chemotherapy alone regardless of the number and location of metastases. In the past, case reports have repeatedly reported survival data of patients who received metastatic and primary tumor resection outside the guidelines. However, there are currently no controlled clinical data from prospective studies that have evaluated the effectiveness of systemic chemotherapy in combination with tumor and metastasis resection in the context of hepatic oligometastasis in pancreatic cancer. Methods: In this single arm, phase-2 trial, survival data from patients receiving neoadjuvant chemotherapy followed by R0/R1 resection will be compared to historic data from patients with oligometastatic adenocarcinoma of the pancreas. Inclusion criteria are patients with a maximum of 5 liver metastases and histology proven PDAC. The combination of liposomal irinotecan (nal-IRI), oxaliplatin (OX) and 5-fluouracil (5-FU)/folinic acid (FA) (Nal-IRIFOX) was chosen as neoadjuvant chemotherapy since recent data suggested superior efficacy and less toxicity compared to mFOLFIRINOX. The primary endpoint is overall survival (OS) after R0/R1 resection. Secondary efficacy endpoints are R0/R1 resection rate and progression-free survival (PFS). Secondary safety endpoints are type, frequency and severity of adverse events with severity according to NCI CTCAE version 5.0 and perioperative morbidity and mortality. Eligible patients with hepatic oligometastatic adenocarcinoma of the pancreas will receive neoadjuvant combination chemotherapy in cycles of 14 days for a duration of 16 weeks in total. In patients with progressive disease during or after the first 4 cycles, neoadjuvant chemotherapy will be permanently discontinued. Patients with tumor response or stable disease after the first 4 cycles according to RECIST v1.1 but a non-resectable primary tumor will receive 4 more cycles. Patients with tumor response or stable disease and a resectable primary tumor after the first 4 cycles will undergo explorative laparotomy and synchronous resection of the tumor and hepatic metastases, if feasible. In total 150 patients will be enrolled for this trial with an aim of 55 patients receiving a complete macroscopic synchronous tumor and metastatic resection. The study is currently ongoing on 11 high-volume centers for pancreatic surgery within Germany. This is the first clinical study to prospectively evaluate the value of multimodality therapy concepts in oligometastatic pancreatic cancer. Clinical trial information: NCT04617457. Research Sponsor: Servier.
Phase II trial of BXCL701 and pembrolizumab in patients with metastatic pancreatic ductal adenocarcinoma (EXPEL-PANC).

Background: Pancreatic ductal adenocarcinoma (PDAC) has limited therapeutic options and is thought to be a “cold” tumor that does not respond to immunotherapy, due to a tumor microenvironment (TME) consisting of a desmoplastic stroma and poor T cell infiltrate. BXCL701 is an oral synthetic dipeptide that competitively inhibits dipeptidyl peptidases DPP4, DPP8, DPP9 and fibroblast activation protein (FAP). BXCL701 exerts antitumor activity via inhibition of DPP8/9, which is associated with induction of proinflammatory cytokines, as well as inhibition of FAP, which disrupts tumor-stromal interactions. Preclinical xenograft models demonstrate synergy between BXCL701 and an anti-PD-1 monoclonal antibody, reducing tumor growth and promoting an increase in intratumoral CD4+ and CD8+ T cells and NK cells. The combination of BXCL701 and pembrolizumab is already being studied in a phase II trial in patients with prostate cancer (NCT03910660) and a multi-cohort basket study (NCT04171219).

Methods: This is a phase II trial of BXCL701 administered at 0.2 mg PO BID days 1-7 and 0.3 mg BID days 8-14 during cycle 1 (21 days) followed by 0.3 mg BID days 1-21 every 21 days in all subsequent cycles, given with pembrolizumab 200 mg IV every 21 days (all cycles). The primary objective is to determine the 18-week progression-free survival rate (PFS18weeks) in patients with metastatic PDAC treated in the second-line setting. We estimate that historical 2nd-line PFS18weeks is 30% or less; using a Simon’s two-stage (minimax) design, a type I error rate of 0.05 and power of 80% when the true response rate of 50%, we will need 19 patients in stage 1 and 20 in stage 2 (a total of 39). We plan to enroll 43 patients to account for a predicted 10% drop out of unevaluable patients. Eligible patients must have metastatic PDAC and disease progression or intolerance to only 1 line of therapy for metastatic disease, without exposure to prior immunotherapy. Patients must have measurable disease amenable to serial biopsies. Correlative pharmacodynamic studies include imaging mass cytometry to examine 34 markers of the PDAC TME in tissue biopsies, as well as blood-based analyses of KRAS circulating tumor DNA, circulating markers of fibrosis, and IL-6. Enrollment began in Q1 2023. Clinical trial information: NCT05558982. Research Sponsor: BioXcel; Merck.
Phase 1b/2 trial of pepinemab plus avelumab as second line combination immunotherapy for patients with metastatic pancreatic adenocarcinoma.

Luis I. Ruffolo, Terrence Lee Fisher, Elizabeth E. Evans, Crystal L. Mallow, Megan Boise, Amber Foster, John E. Leonard, Brian A. Belt, Jen Jen Yeh, Maurice Zauderer, David Linehan, Daniel Mulkerin; University of Rochester Cancer Center & Wilmot Cancer Institute, Rochester, NY; Vaccinex, Inc., Rochester, NY; University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Monotherapy with immune checkpoint inhibitors (ICIs) is not effective in metastatic pancreatic adenocarcinoma (PDAC), likely due to the unique immunosuppressive tumor microenvironment (TME) of PDAC, thus safe and novel strategies to overcome resistance and facilitate adaptive immune responses are a major unmet need. Preclinical and clinical studies demonstrated that antibody blockade of semaphorin 4D (SEMA4D) promotes tumor infiltration and activation of DCs and CD8+ T cells and reverses immunosuppression, including attenuation of MDSC recruitment and function, leading to enhanced efficacy of ICIs without increasing toxicity. Pepinemab, a SEMA4D blocking antibody, in combination (combo) with avelumab provided clinical benefit in some patients with ICI-resistant and PD-L1-low NSCLC (NCT03268057). Pepinemab is also being evaluated in combo with pembrolizumab in patients with metastatic squamous cell carcinoma of the head and neck (NCT04815720). The principal goals of this proof-of-concept study are to investigate the safety, efficacy, and TME biomarker changes of treatment with the combo of pepinemab plus avelumab in patients with metastatic PDAC.

Methods: This single-arm, open-label study (NCT05102721) is evaluating the safety, tolerability, and efficacy of pepinemab in combo with avelumab in patients diagnosed with metastatic PDAC who have either progressed on or are otherwise intolerant to first line chemotherapy. Patients must have received 5FU or gemcitabine-based first line therapy with evidence of intolerance or treatment failure, including progression both during or after completing first-line treatment. Accrual for the Phase 1b portion follows a Bayesian Optimal Interval Design (BOIN), beginning at the highest dose combo; 20 mg/kg pepinemab and 800 mg avelumab Q2W. Phase 2 begins after 16 subjects are enrolled at MTD, permitting a Simon’s two stage assessment of futility prior to closing the Phase 1b period. The primary objective for Phase 1b is tolerability, and the primary objective for Phase 2 is therapeutic efficacy compared to historical second-line systemic chemotherapy. The trial anticipates a total evaluable cohort of 40 subjects and is powered to detect a response rate of 23% or greater, with alpha set at 0.1 and 80% power. Exploratory objectives include robust correlative analysis of immune, stromal, and genomic profiling of baseline and on-treatment tumor biopsies to ascertain mechanisms of treatment response and failure. Patient reported outcomes are incorporated throughout the trial to assess disease specific symptoms associated with pancreatic cancer and cancer cachexia. One patient has been enrolled as of Feb 14, 2023. Clinical trial information: NCT05102721. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Vaccinex, Inc.; U.S. National Institutes of Health.
A phase 1 study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of LB4330, a peptide fused to CLDN18.2 antibody targeting the tumor antigen associated CD8+ T CELLS in patients with advanced solid tumors.

Jiajian Liu, L&L Team; Shanghai, China

Background: PD-1/PD-L1-targeted immunotherapies have become critical roles in the treatment for many tumors. However, there is limited progress in pancreatic ductal adenocarcinoma (PDAC). PDAC is low immunogenicity. PDAC microenvironment is immunosuppressive. More than 70% PDACs have few or no CD8+ T cells around the tumor cell or in the tumor microenvironment (TME). Therefore, immunotherapy like PD-1/PD-L1 antibody alone is rarely effective for PDACs. Some cytokine or analogs may activate CD8+ T cells. An analog specifically activating tumor antigen associated (TAA) CD8+ T cells was designed and fused to anti-CLDN18.2 antibody. This specific bi-functional molecule LB4330 has high affinity to human anti-CLDN18.2 (14pM) and CD8+T cells. LB4330, as a novel, first-in-class molecule, may activate TAA CD8+ T cells in TME and has potential in alone or in combination with PD-1/PD-L1 mAb, for the treatment of advanced solid tumors, especially for Claudin 18.2 positive PDAC.

Methods: This is a FIH, phase 1 study to evaluate the safety, tolerability, pharmacokinetics and immunogenicity of LB4330 in patients with advanced solid tumors (MEETCD8-001). The planned sample size is approximately 66 patients in two parts: part 1 dose escalation, will evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D). Part 2 dose expansion will further characterize the safety profile and preliminary tumor response in advanced gastric and gastroesophageal junction adenocarcinoma and PDAC with Claudin 18.2 expression. In dose escalation stage, patients will be recruited with advanced solid tumors who have failed standard treatment, or for whom standard treatment is not available or applicable at this stage. Exclusion criteria include a greater risk for gastric bleeding, irritable bowel syndrome with symptoms, active virus infections. The primary endpoints are incidence of dose limiting toxicities and adverse events, MTD, and recommended phase 2 dose. Secondary objectives will evaluate PK parameters, preliminary antitumor activity, and immunogenicity of LB4330. Tumor response will be assessed per RECIST and iRECIST every 2 cycles. The Phase I study in advanced solid tumors is ongoing. Enrollment in cohort 1 began in Nov 2022. Clinical trial information: NCT05707676. Research Sponsor: L&L Biopharma Co., LTD., Shanghai, China.
ASCEND: A randomised, double-blinded, phase II study of gemcitabine and nab-paclitaxel with CEND-1/LSTA1 or placebo in patients with untreated metastatic pancreatic ductal adenocarcinoma.

Background: LSTA1 is a novel cyclic peptide with high tumor vascular endothelium specificity that activates an endocytotic/exocytotic transport pathway on stroma and tumor. LSTA1 potentiates greater intratumoral access for co-administered or tethered anti-cancer agents, including small molecules, antibodies, and nanoparticles, leading to increased anti-neoplastic activity. Preclinical studies in solid tumor models have shown co-administering LSTA1 is effective in augmenting the delivery and activity of multiple anti-cancer agents. LSTA1 has been evaluated in 31 patients in a Phase I study in metastatic pancreatic ductal adenocarcinoma (mPDAC) demonstrating an objective response in 59% of patients, a 79% disease control rate at 16 weeks with a median progression free survival (PFS) of ~9.9 months. No dose limiting toxicities were observed. The ASCEND study will determine whether LSTA1 when added to SOC chemotherapy is active and safe as first-line treatment of mPDAC, and whether an additional dose of LSTA1 administered approximately 4 hours after chemotherapy further improves anti-cancer activity.

Methods: ASCEND is a randomized, double-blind, placebo-controlled phase II trial evaluating the safety and efficacy of LSTA1 3.2 mg/kg in combination with standard of care chemotherapy (nab-paclitaxel 125mg/m² and gemcitabine 1000mg/m² on days 1, 8, and 15, every 28 days) in patients with histologically proven, previously untreated mPDAC. A total of 155 subjects will be randomized 2:1 in favor of study intervention in two cohorts and stratified by age, ECOG status, presence of liver metastasis, and study site. Patients in cohort A receive single doses of LSTA1 or placebo, and for cohort B, two doses of LSTA1 or placebo spaced 4 hours apart. Tumour assessment occurs every 8-weeks from randomization until disease progression or commencement of a new anti-cancer therapy. The primary endpoint is PFS. Secondary endpoints include objective tumour response safety, overall survival, and patient reported outcomes. At 14 Feb 2023, 70 participants have been enrolled from Australian sites. Sites in Ireland and New Zealand are anticipated to open this year. Clinical trial information: NCT05042128. Research Sponsor: Lisata Therapeutics, Inc.
Randomized phase II trial of olaparib + pembrolizumab vs olaparib alone as maintenance therapy in metastatic pancreatic cancer patients with germline BRCA1 or BRCA2 (gBRCA1/2+) pathogenic variants: SWOG S2001.

Vincent Chung, Katherine A Guthrie, Michael J Pishvaian, Kim Anna Reiss, Andrew M. Lowy, Davendra Sohal, Sarah Colby, Elad Sharon, Carmen Joseph Allegra, Eileen Mary O’Reilly, E. Gabriela Chiorean, Philip Agop Philip; City of Hope, Duarte, CA; Fred Hutchinson Cancer Research Center, and SWOG Statistics and Data Management Center, Seattle, WA; Johns Hopkins University School of Medicine, Washington, DC; University of Pennsylvania, Philadelphia, PA; UC San Diego Moores Cancer Center, La Jolla, CA; University of Cincinnati, Cincinnati, OH; SWOG Statistical Center, Seattle, WA; Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD; Cancer Therapy Evaluation Program, Division of Cancer Treatment & Diagnosis, National Cancer Institute of the National Institutes of Health, Bethesda, MD; Memorial Sloan Kettering Cancer Center, New York, NY; University of Washington, Seattle, WA; Hoag Family Cancer Institute, Newport Beach, CA

Background: Olaparib was approved in 2019 as maintenance therapy for gBRCA1/2+ metastatic pancreatic cancer (mPDA) patients (pts). The POLO trial showed an improvement in median progression-free survival (mPFS) with olaparib compared to placebo (7.4 vs 3.8 months) for platinum sensitive gBRCA1/2+ mPDA pts. Preclinical studies have demonstrated that PARP inhibitors modulate the immune microenvironment by increasing genomic instability, PD-L1 expression and activating the immune inflammatory stimulator of interferon genes (STING) pathway. Several clinical studies in solid tumors have shown preliminary efficacy with the combination of PARP plus immune checkpoint inhibitors. Based upon these data, SWOG S2001 aims to further improve the PFS of gBRCA1/2+ mPDA pts.

Methods: S2001 was developed in collaboration with the Alliance and was activated in SWOG in December 2020. Key eligibility criteria include: mPDA pts with gBRCA1/2 pathogenic variants identified with standard of care germline genetic testing and progression-free after receiving at least 16 weeks of platinum-based chemotherapy (FOLFIRINOX, FOLFOX or gemcitabine/cisplatin +/- nab-paclitaxel). One cycle of gemcitabine and nab-paclitaxel is allowed while waiting for germline testing. Zubrod performance status (PS) 0 or 1 pts are eligible. Pts are stratified according to first line chemotherapy, PS 0 vs 1, and disease status after 1st line treatment. The primary objective of this study is to compare PFS in mPDA pts treated with olaparib + pembrolizumab versus olaparib alone as maintenance therapy. Based upon the POLO trial, we expect a mPFS of 7 months in the control arm. Targeting a mPFS of 11.7 months in the experimental arm (hazard ratio 0.6) and assuming 15 months follow-up, 80% power and a 1-sided alpha=0.10, this design requires enrolling 88 pts for a total of 78 eligible and evaluable pts. As of February 2023, 26 participants have been accrued. Prospective serial blood samples will be collected to bank DNA and RNA for future correlative studies. Clinical trial information: NCT04548752. Research Sponsor: U.S. National Institutes of Health.
Phase 3 PANOVA-3 study: Tumor treating fields (TTFields) therapy concomitant with gemcitabine and nab-paclitaxel (GnP) for front-line treatment of locally advanced pancreatic cancer.

Hani M. Babiker, Teresa Macarulla, Philip Agop Philip, Carlos Roberto Becerra, Tomislav Dragovich, Vincent J. Picozzi; Mayo Clinic Florida, Jacksonville, FL; Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; Karmanos Cancer Institute, Detroit, MI; Hoag Family Cancer Institute, Newport Beach, CA; Banner MD Anderson Cancer Center, Gilbert, AZ; Virginia Mason Hospital and Medical Center, Seattle, WA

Background: Tumor Treating Fields (TTFields) therapy is a locoregional antimitotic treatment approved for newly diagnosed and recurrent glioblastoma GBM and pleural mesothelioma. TTFields (150 kHz) therapy, with/without chemotherapy, had antiproliferative and anticlonogenic activity in pancreatic cancer cell lines, and reduced tumor volume and weight more than chemotherapy alone in in vivo models. TTFields therapy with gemcitabine and nab-paclitaxel (GnP) was well-tolerated, with promising efficacy in metastatic and locally advanced pancreatic adenocarcinoma (LAPC) in the phase 2 PANOVA study (NCT01971281). LAPC prognosis remains poor despite available therapies, which can negatively impact quality of life (QoL). As such, there remains a need for effective and tolerable treatments. Methods: PANOVA-3 (EF-27, NCT03377491) is a prospective, randomized, phase 3 study investigating the efficacy and safety of TTFields therapy with GnP in patients with LAPC, with a planned enrollment of 556 patients. Key inclusion criteria are: a diagnosis of unresectable LAPC (per NCCN guidelines), ECOG PS of 0–2, and no prior treatment. Patients will be stratified by performance status and geographical region and assigned 1:1 to treatment groups to receive TTFields therapy + GnP or GnP alone. GnP will be administered at a standard dose per standard of care. TTFields therapy (150 kHz, 18h/day) will be delivered by the NovoTTF-200T System until local disease progression per RECIST v1.1. Usage will be tracked by the device. Follow-up will be performed every 4 weeks and computed tomography scans of the chest and abdomen will be taken every 8 weeks until disease progression. Patients will be followed every month until death. The primary endpoint is overall survival and key secondary endpoints include QoL, pain-free survival, and puncture-free survival, which will be compared between treatment groups. Other secondary endpoints include progression-free survival (PFS), local PFS, objective response rate, 1-year survival rate, rate of resectability, and safety. Guidance around usage, lifestyle integration and prevention and management of skin adverse events will be provided by Device Support Specialists and field personnel. Usage information will be provided to patients and physicians to facilitate discussions to optimize outcomes by maximizing time on therapy. Together, these novel support approaches aim to optimize patient usage and outcomes. The trial is currently recruiting at 149 sites, globally. The DMC last reviewed the trial in August 2022, and suggested that the trial continue as planned. Clinical trial information: NCT03377491. Research Sponsor: Novocure.
CheMo4METPANC: A phase 2 study with combination chemotherapy (gemcitabine and nab-paclitaxel), chemokine (C-X-C) Motif receptor 4 inhibitor (motixafortide), and immune checkpoint blockade (cemiplimab) in metastatic treatment-naïve pancreas adenocarcinoma.

Gulam Abbas Manji, Michael S. May, Ilenia Pellicciotta, Sarah Sta Ana, Naomi Sender, Samuel M Pan, Isabelle Ross, Jianhua Hu, Qian Shi, Alexander G Raufi; Columbia University Medical Center/New York-Presbyterian Hospital, New York, NY; Columbia University Medical Center, New York, NY; Columbia University, New York, NY; Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY; Department of Quantitative Science Research, Mayo Clinic, Rochester, MN; Brown University School of Medicine-Rhode Island Island Hospital, Providence, RI

Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a uniformly fatal disease for which treatments result in limited benefit. Failure of immune checkpoint blockade is attributed to multiple immunosuppressive pathways within the tumor microenvironment. The C-X-C motif chemokine receptor 4 (CXCR4)/C-X-C motif chemokine ligand 12 (CXCL12) axis results in exclusion of anti-tumor immune cells. Preclinical studies demonstrated that simultaneous CXCR4 inhibition (CXCR4i) and anti-programmed cell death 1 (aPD1) resulted in tumor stabilization. We extended these findings by testing multiple combinations of CXCR4i, aPD1, and gemcitabine in the KPC mouse model of PDAC. Mice treated with gemcitabine, CXCR4i, and aPD1 (triple therapy) experienced a survival benefit compared to mice treated with either gemcitabine alone, or with CXCR4i/aPD1. Tumors from mice treated with triple therapy demonstrated increased apoptosis and a favorable tumor immune microenvironment (TIME). Motixafortide with pembrolizumab, fluorouracil, and nanoliposomal irinotecan has shown encouraging results in the second-line setting in mPDAC with a confirmed ORR of 13.2% and progression free survival (PFS) of 3.8 months (m). The goal of this first-in-man trial is to test preliminary safety and efficacy of Motixafortide (CXCR4i), Cemiplimab (aPD1), Gemcitabine, and Nab-paclitaxel (MCGN) in treatment naive mPDAC. Methods: This is an open label, multicenter, investigator-initiated simon-2-stage phase 2 clinical trial in mPDAC testing MCGN. The study includes a six-patient safety run-in cohort and an additional 4 patients comprising a pilot efficacy signal seeking study (N=10). If ≥3 of the 10 patients within the pilot stage were to experience a partial response (PR) by RECIST criteria within 16 weeks, the combination would be considered promising and an expansion cohort of an additional 30 patients was planned. On 09/21/22, we amended the study to forego the planned open-label expansion cohort (N=30) and transition directly to a randomized phase 2 trial testing MCGN compared toGemcitabine and Nab-paclitaxel (GN) alone (N=102), after completion of the pilot phase of the study. The primary endpoint is PFS. The study has 80% power to detect an improvement in PFS from 6 to 9.2 m (HR 0.65) with a one-sided alpha of 0.20. One interim analysis for futility is planned when 50% of the PFS events are observed. Secondary objectives include ORR, disease control rate, duration of clinical benefit and OS. Required (pilot portion) and optional (randomized portion) paired tumor biopsies will undergo exploratory analysis including interrogation of the TIME. This trial was started in September 2020 and has enrolled 10 patients to the pilot stage as of 02/2023. Clinical trial information: NCT04543071. Research Sponsor: Regeneron Pharmaceuticals; BioLineRx.
A phase 1b, open-label, two-part safety, tolerability, and efficacy study of a soluble beta-glucan (odetiglucan) in combination with a CD40 agonistic monoclonal antibody (CDX-1140) in patients with metastatic pancreatic adenocarcinoma whose disease did not progress during first-line (1L) chemotherapy.

Mark H. O’Hara, Max Miller Wattenberg, Ignacio Garrido-Laguna, Eileen Mary O’Reilly, Michael Jay Yellin, Tibor Keler, Michele Anne Gargano, Nick Niles, Jeremy Drees, Nandita Bose, Jose Luis Iglesias, Gregory Lawrence Beatty; Hospital of the University of Pennsylvania, Philadelphia, PA; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Memorial Sloan Kettering Cancer Center, New York, NY; Celldex, Hampton, NJ; Celldex Therapeutics, Inc., Hampton, NJ; HiberCell, Fairview, MN; HiberCell, Inc., New York, NY; APEX Oncology Consulting, Inc., Oakville, ON, Canada

Background: Metastatic pancreatic ductal adenocarcinoma (PDAC) is an aggressive and lethal disease with a 5-year overall survival (OS) rate of 3%. Standard of care treatment is continuous cytotoxic chemotherapy which produces modest improvements in OS but is also associated with significant toxicity raising the need for novel treatment paradigms. Although immunotherapy has yet to produce clinical benefit for most patients with PDAC, preclinical modeling demonstrates its potential and show that combinations of myeloid agonists can trigger robust synergistic anti-tumor activity against PDAC tumors that are otherwise resistant to immunotherapy including immune checkpoint blockade (anti-CTLA4, anti-PD1). In this study, odetiglucan (OD), a novel beta glucan pathogen associated molecular pattern (PAMP), will be combined for the first time with CDX-1140, a fully human Ig2K agonistic monoclonal CD40 antibody in the maintenance setting after an induction phase of cytotoxic chemotherapy. OD and a CD40 agonist directly promote the activation and maturation of antigen presenting cells and shift the suppressive TME to enhance T-cell responses through non-redundant myeloid signaling pathways. We hypothesize that the combination of OD and CD40 agonist therapy has the potential to trigger anti-tumor immunity in PDAC and thus, extend and deepen responses to 1L cytotoxic chemotherapy.

Methods: A two-part Phase 1b study of metastatic PDAC pts who have evidence of response or stable disease following 16-24 wks of chemotherapy is being conducted. Part A uses a 3+3 design; pts will receive OD 4 mg/kg QW + CDX-1140 1.5 mg/kg Q3W. Following a dose-limiting toxicity observation period, the dose will be held at 1.5 mg/kg or decreased to 0.72 mg/kg Q3W. Once preliminary safety is established, the cohort will be expanded to 15 pts. Part B pts will receive OD 4mg/kg + CDX-1140 at the dose identified in Part A Q3W. The study will enroll 30 pts. Main eligibility criteria: Metastatic PDAC having durable stable disease or response to 1L chemotherapy; serum ABA ≥20 µg/mL, and no prior anti-CD40 mAb or immunomodulatory treatment exposure. Primary endpoints are MTD, RP2D, and safety. Secondary endpoints include DOR, PFS, ORR, and OS and exploratory endpoints include evaluating immune pharmacodynamic responses in peripheral blood and tumor. Safety parameters will be listed and summarized using descriptive statistics. ORR will be tabulated by overall frequency; DOR, TTF, PFS and OS will be summarized and presented using Kaplan-Meier and waterfall plots. 5 US sites will participate. Clinical trial information: NCT04834778.

Research Sponsor: HiberCell.
Apollo: A randomized phase II double-blind study of olaparib versus placebo following curative intent therapy in patients with resected pancreatic cancer and a pathogenic BRCA1, BRCA2, or PALB2 mutation—ECOG-ACRIN EA2192.

Kim Anna Reiss, Sung Chul Hong, Anup Kasi, Eileen Mary O’Reilly, Shishir K. Maithel, Xin Yao, Stanley R. Hamilton, Ben Boursi, Michael J. Pishvaian, Samuel J Klempner, Susan M. Domchek, Paul J. Catalano, E. Gabriela Chiorean, Philip Agop Philip, Peter J. O’Dwyer; University of Pennsylvania, Philadelphia, PA; Dana-Farber Cancer Institute, Boston, MA; University of Kansas Cancer Center, Westwood, KS; Memorial Sloan Kettering Cancer Center, New York, NY; Winship Cancer Center of Emory University, Atlanta, GA; Cleveland Clinic Martin Health Florida, Stuart, FL; City of Hope National Medical Center, Duarte, CA; Sheba MC, Ramat Gan, Israel; Johns Hopkins University School of Medicine, Washington, DC; Mass General Cancer Center, Boston, MA; Basseter Center for BRCA, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; University of Washington, Seattle, WA; Hoag Family Cancer Institute, Newport Beach, CA; University of Pennsylvania Department of Medicine, Philadelphia, PA

Background: A meaningful subset of PDAC is characterized by a homologous recombination deficiency (HRD). The most well-defined patients within this group are those with pathogenic variants in BRCA1, BRCA2 and PALB2. In the metastatic setting, PARP inhibitor maintenance provides a progression-free survival benefit after a period of platinum based chemotherapy1,2, but the role of PARP inhibitors in the curative intent setting is undefined. The OlympiA study established one year of olaparib as the standard of care for patients with BRCA-related, early stage breast cancer who completed all other curative-intent treatment3. Therefore, we have designed a randomized, phase II double-blind study of one year of olaparib vs placebo in patients with pancreatic cancer and a germline or somatic variant in BRCA or PALB2 who have completed all curative intent therapy. Methods: We have enrolled and treated 29 of 152 planned patients on study NCT 04858334/EA2192. Eligibility criteria include: a pathogenic germline or somatic variant in BRCA1, BRCA2 or PALB2 as determined by local laboratory (central review required); completion of curative-intent resection and ≥ three months of multi-agent chemotherapy; no evidence of recurrent disease. At enrollment, patients must be within 12 weeks of their last anti-cancer intervention. Patients are randomized 2:1 to receive oral olaparib 300 mg twice daily or placebo for 12 28-day cycles. The primary endpoint is relapse-free survival. Overall survival is a secondary endpoint. Tumor tissue, fecal material (for microbiome analysis) and serial ctDNA samples are being collected. 1) Golan T, Locker GY, Kindler HL: Maintenance Olaparib for Metastatic Pancreatic Cancer. Reply. N Engl J Med 381:1492-1493, 2019. 2) Reiss KA, Mick R, O’Hara MH, et al: Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in BRCA1, BRCA2, or PALB2. J Clin Oncol 39:2497-2505, 2021. 3) Tutt ANJ, Garber JE, Geyer CE, Jr.: Adjuvant Olaparib in BRCA-Mutated Breast Cancer. Reply. N Engl J Med 385:1440, 2021. Clinical trial information: NCT04858334. Research Sponsor: U.S. National Institutes of Health; PANCAN.
ExoLuminate: An observational registry study for detection of pancreatic adenocarcinoma (PDAC) in high-risk or clinically suspicious patients.

Harmeet Dhani, Juan Pablo Hinestrosa, Jesus Izaguirre Carbonell, Heath Balcer, Razelle Kurzrock, Paul R. Billings; Biological Dynamics, Inc., San Diego, CA; Medical College of Wisconsin and WIN Consortium, Milwaukee, WI

Background: The detection of pancreatic ductal adenocarcinoma (PDAC) at early-stages is critical to improving patient survival. However, the lack of a clinically useful biomarker assay poses a challenge for earlier detection. A liquid biopsy test (ExoVita Pancreas) which uses extracellular vesicles (EV) protein biomarkers has been developed for detection of PDAC. In a previous case-control study of n=715 (75 cases of PDAC Stage I and II, 640 controls), the EV-protein biomarker assay yielded a sensitivity of 96.0% and specificity of 91.1%. By optimizing the assay for high sensitivity, we aim to generate evidence for earlier detection of PDAC in high-risk and clinically suspicious patients in the hope of impacting PDAC patient diagnostic journeys. Methods: ExoLuminate is a prospective, multi-center, observational registry study to demonstrate that early detection of PDAC using ExoVita is non-inferior to current standard of care methods of surveillance. The study duration will be 36 months (24-month accrual, 12-month follow-up), with a minimum of 1000 subjects to be enrolled between two cohorts as described below. The first cohort enriches for “high-risk” individuals without a cancer suspicion or diagnosis including those with intraductal papillary mucinous neoplasms (IPMNs), personal or family history of pancreatitis, family member(s) who have at least one first-degree relative affected by pancreatic cancer, patients over 50 years of age with new-onset diabetes (NOD), and germline mutations known to be associated with PDAC. The second cohort includes patients with clinical findings suspicious for early-stage PDAC or those with biopsy-proven PDAC. Patients enrolled in the study will have their blood obtained at six-month intervals. The performance of ExoVita liquid biopsy will be compared to standard-of-care imaging and biomarkers such as CA19-9. Through this registry, which began enrollment in December 2022 and is open for accrual (NCT0562552), we aim to demonstrate the clinical utility of a novel liquid biopsy based on detection of EV-derived biomarkers for early diagnosis of PDAC which can provide credence to a new paradigm in early detection to improve patient outcomes. Clinical trial information: NCT0562552. Research Sponsor: Biological Dynamics, Inc.
Alliance A021806: A phase III trial evaluating perioperative versus adjuvant therapy for resectable pancreatic cancer.

Akhil Chawla, Qian Shi, Andrew H. Ko, Shaalan Beg, Anna M. Varghese, Stephen W Behrman, Mark Bloomston, Firas Salem Ahmed, Wendy L. Frankel, Jesse G. Dixon, Xiomara W. Carrero, Ardaman Shergill, Jamie Crawley, Oguz Akin, Daniel John Renouf, George Zogopoulos, Joleen M. Hubbard, Jeffrey A. Meyerhardt, Eileen Mary O'Reilly, Cristina R. Ferrone; Northwestern University Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; UT Southwestern/Simmons Cancer Center, Dallas, TX; Memorial Sloan Kettering Cancer Center, New York, NY; University of Tennessee Health Science Center, Memphis, TN; South Florida Surgical Oncology, Fort Myers, FL; Columbia University Medical Center, New York, NY; The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Department of Medicine, Section of Hematology & Oncology, University of Chicago Medical Center, Chicago, IL; University of Chicago, Chicago, IL; BC Cancer Agency, University of British Columbia, Vancouver, BC, Canada; McGill University Health Centre, Montreal, QC, Canada; Department of Medical Oncology, Mayo Clinic, Rochester, MN; Alliance for Clinical Trials in Oncology, Chicago, IL; Massachusetts General Hospital, Boston, MA

Background: The role of neoadjuvant chemotherapy in resectable pancreatic cancer has yet to be defined. Recent phase II trial results demonstrate a median overall survival time (mOS) of only 22.4 months after treatment with perioperative modified FOLFIRINOX (mFOLFIRINOX) with 36% not reaching surgery due to disease progression during neoadjuvant therapy. While potential benefits and shortcomings of neoadjuvant chemotherapy have been well documented, to date, no phase III trial has directly compared a perioperative versus an adjuvant chemotherapy strategy in resectable pancreatic cancer. Alliance for Clinical Trials in Oncology A021806 is an actively accruing randomized controlled phase III trial evaluating the efficacy of perioperative chemotherapy with mFOLFIRINOX in patients with resectable pancreatic cancer. Methods: To qualify for enrollment, patients must have biopsy-proven localized resectable pancreatic adenocarcinoma as defined by the National Comprehensive Cancer Network. Patients must have good performance status (ECOG 0 or 1) and be candidates to receive mFOLFIRINOX treatment. All patients enrolled undergo central radiologic eligibility review for quality control and are then randomized to either Arm 1 which consists of 8 cycles of neoadjuvant mFOLFIRINOX followed by 4 cycles of adjuvant mFOLFIRINOX or Arm 2 which includes upfront surgery followed by 12 cycles of adjuvant mFOLFIRINOX. The primary endpoint of the trial is overall survival with secondary endpoints evaluating disease-free survival, margin-negative resection rate, surgical complications, and chemotherapeutic adverse events. Additional correlative endpoints include quality of life and radiomic imaging assessments. A total enrollment of 352 patients is planned from the US and Canada; current enrollment for this trial is at 145 patients. An OS interim analysis will be performed when 50% of the events (124) are observed combining the two arms. If the trial continues after interim analysis, the final OS analysis will be performed with a total of 248 events (combined arms). If the Cox model (stratified by tumor location and ECOG PS) comparing OS between arms produces a one-sided p-value < 0.05, then we will conclude that the OS of the perioperative therapy arm is superior to adjuvant therapy. The Alliance A021806 phase III trial aims to define a new standard of care for patients with resectable pancreatic cancer. Clinical trial information: NCT04340141. Research Sponsor: U.S. National Institutes of Health; U10CA180821, U10CA180882; U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG); U10CA180888 (SWOG).
Targeting minimal residual disease (MRD) in resected RAS mutated pancreatic cancer with vaccine TG01/QS-21 +/- PD-1 inhibitor, balstilimab: A randomized phase II study (TESLA).

Anup Kasi, Francisco Diaz, Raed Moh’d Taiseer Al-Rajabi, Joaquina Celebre Baranda, Erin Carroll, Cathey Belcher, Mojtaba Olyaee, Amit Rastogi, Timothy Schmitt, Sean Kumer, Atta Nawabi, Harsh B Pathak, Andrew K. Godwin, Mary Markiewicz, Weijing Sun; University of Kansas Cancer Center, Westwood, KS; University of Kansas Medical Center (KUMC), Kansas City, KS; University of Kansas, Kansas City, KS; University of Kansas Medical Center, Kansas City, KS

Background: MRD detected by presence of circulating tumor DNA (ctDNA) after intended curative treatment is associated with high risk of relapse in pancreatic cancer. Early treatment of patients with presence of ctDNA after completion of surgery +/- adjuvant therapy may offer an opportunity to clear ctDNA and improve outcomes. TG01 is a RAS-neoantigen peptide vaccine adjuvanted by QS-21 (Stimulon) targeting the seven most frequent codon 12-13 RAS mutations. TG01 has previously demonstrated ability to activate mutant RAS specific CD4+ and CD8+ T-cell responses in vaccinated patients and repeated TG01 dosing in resected pancreatic cancer was found to be well tolerated and associated with a median OS of 33.4 months (95% CI 24.0, 45.8)1,2. Checkpoint inhibitors as single agents have not shown anti-tumor activity in pancreatic cancer, suggesting that a priming agent inducing tumor-specific T-cells may be required to support efficacy. Balstilimab is a human monoclonal antibody targeting programmed cell death protein 1 (PD-1) which is intended to reverse the immunosuppressive effects of this signaling pathway in the context of tumor immuno-surveillance by T-cells.

Methods: Design: A two-arm, open-label, phase II randomized trial of TG01/QS-21 vaccine or TG01/QS-21 vaccine plus balstilimab (n=12 per arm, N=24) with surgically resected Stage 1-3 RAS mutant PDAC who are MRD+ following completion of standard adjuvant chemotherapy. Assay: MRD is detected by a commercially available ctDNA assay (Signatera, Natera). Somatic variants are identified by whole-exome sequencing of the primary tumor and the matched normal (whole blood) sample and a bespoke assay of up to 16 clonal, somatic variants are generated for each patient. This “tumor signature” will be monitored in plasma throughout the study. Treatment schedule: A priming phase of six vaccine administrations once every two weeks followed by a maintenance phase of administrations once every 8 weeks for up to 51 weeks. Balstilimab will be administered every 2 weeks for up to 51 weeks beginning at week 3. Imaging assessment will be done every 12 weeks. Eligibility: Surgically resected pancreatic adenocarcinoma with pathogenic RAS mutation, and no evidence of recurrent disease on baseline imaging. Inclusion criteria also include ECOG PS 0-1, and positive Signatera ctDNA MRD. Objectives: The primary objective is to assess the 6-month molecular disease control rate as defined by ctDNA stable, decreased or cleared. Secondary objectives include safety of TG01/QS-21 with or without balstilimab, 6 and 12-month DFS rate in each cohort, as well as correlation between the depth of molecular response and DFS. Exploratory: changes in clonality of RAS mutations and assess immune response. Enrollment is ongoing. 1) Gjertsen MK et al. Int J Cancer 1997, 72(5) 784-90. 2) Palmer DH et al. Br J Cancer 2020 122:971-77. Clinical trial information: NCT05638698. Research Sponsor: Targovax.
STAR-221: A randomized, open-label, multicenter, phase 3 trial of domvanalimab, zimberelimab, and chemotherapy versus nivolumab and chemotherapy in previously untreated, locally advanced, unresectable or metastatic gastric, gastroesophageal junction, and esophageal adenocarcinoma.

Samuel J Klempner, Kohei Shitara, Allan Sison, Jennifer Scott, Dana Wishengrad, Jack Ronayne, Joon Rhee, Siddhartha Mitra, Dimitry S. A. Nuyten, Yelena Y. Janjigian, Zev A. Wainberg; Mass General Cancer Center, Boston, MA; National Cancer Center Hospital East, Kashiwa, Japan; Arcus Biosciences, Hayward, CA; Gilead Sciences, Inc., Foster City, CA; Memorial Sloan Kettering Cancer Center, New York, NY; UCLA School of Medicine, Los Angeles, CA

Background: The addition of programmed cell death/ligand protein 1 (PD-L1) inhibitors to standard chemotherapy has improved outcomes in patients with HER2-negative unresectable or metastatic esophago-gastric adenocarcinomas. Current first-line (1L) treatment for these patients comprises FOLFOX (oxaliplatin, leucovorin, and fluorouracil) and CAPOX (capecitabine and oxaliplatin) chemotherapy, with or without the addition of a PD-1 inhibitor. Domvanalimab (dom) is an Fc-silent humanized IgG1 monoclonal antibody (mAb) that blocks T cell Immunoglobulin and ITIM domains (TIGIT), reducing immunosuppression of T/natural killer (NK) cells and promoting antitumor activity. Zimberelimab (zim) and nivolumab are mAbs that bind to PD-1 on T/NK cells, preventing the immunosuppressive effects of PD-L1 and leading to enhanced immune-mediated tumor cell death. Prior studies (including ARC-7) have demonstrated that the combination of dom + zim is safe, tolerable, and has promising activity in patients with lung cancer and esophago-gastric cancers. This study will investigate whether adding anti-TIGIT therapy to the standard combination of anti-PD-1 therapy and chemotherapy in patients with locally advanced unresectable or metastatic gastric, GEJ, and esophageal adenocarcinoma provides additional clinical benefit. Methods: STAR-221 (NCT05568095) is a global, phase 3, randomized, open-label study. Eligible patients are adults with locally advanced unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma treated in the 1L setting with ≥1 measurable lesion(s) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with known HER2-positive tumors are not eligible. Approximately 970 patients will be randomized 1:1 into 1 of 2 treatment arms. Patients randomized to Arm A will receive either dom 1600 mg + zim 480 mg every 4 weeks (Q4W) in addition to FOLFOX chemotherapy once every 2 weeks (Q2W) or dom 1200 mg + zim 360 mg once every 3 weeks (Q3W) in addition to CAPOX chemotherapy Q3W. Patients randomized to Arm B will receive either nivolumab 240 mg Q2W + FOLFOX Q2W or nivolumab 360 mg Q3W + CAPOX Q3W. Randomization will be stratified by PD-L1 expression (tumor area positivity [TAP] ≥ 5% vs TAP < 5%), ECOG performance status (0 vs 1), and region (USA, Canada, and EU5 countries vs Asia vs rest of world). The dual primary endpoints are overall survival (OS) in the intent-to-treat population and OS in patients with high PD-L1 expression (TAP ≥ 5%). Secondary endpoints include progression-free survival, objective response rate, duration of response, and safety and tolerability. STAR-221 is currently enrolling globally. Clinical trial information: NCT05568095. Research Sponsor: Arcus Biotech.