Recommended Hepatobiliary Cancer Abstracts from ASCO 2019
Pembrolizumab (pembro) for advanced biliary adenocarcinoma: Results from the KEYNOTE-028 (KN028) and KEYNOTE-158 (KN158) basket studies.

Abstract No: 4079

Background: Antitumor activity with pembro, an anti–PD-1 antibody, has been observed in patients (pts) with advanced/metastatic biliary tract cancers (BTC), who have limited treatment options. We present follow-up data from pts with advanced BTC treated with pembro in the KN158 (NCT02628067; phase 2) and KN028 (NCT02054806; phase 1) studies.

Methods: Eligible pts ≥18 y in the KN158/KN028 BTC cohorts had histologically/cytologically confirmed incurable advanced BTC that progressed after/failed any number of prior standard treatment regimens, measurable disease per RECIST v1.1, ECOG PS of 0/1, and no prior immunotherapy. PD-L1–positivity (membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma) was required for eligibility in KN028, but not KN158. Pts received pembro 200 mg Q3W (KN158) or 10 mg/kg Q2W (KN028) for up to 2 y. Radiographic imaging occurred Q9W for 12 mo (KN158) or Q8W for 6 mo (KN028) and Q12W thereafter. Primary efficacy endpoint in both studies was ORR by RECIST 1.1. Response assessed by independent central review is reported.

Results: Median (range) follow-up was 7.5 (0.6–29.5) mo in the 104 pts from KN158 and 6.5 (0.6–33.1) mo in the 24 pts from KN028 with BTC. All pts in KN028 and 61 in KN158 had PD-L1–positive tumors. No pt had MSI-H tumors (not assessed in KN028). In KN158, ORR was 5.8% (6/104, all PR [including 1 pt with PD-L1–negative tumor]; 95% CI, 2.1%–12.1%) and median duration of response (DOR) was not reached (NR; range, 6.2 to 23.2+ mo). Median OS and PFS were 7.4 mo (95% CI, 5.5–9.6) and 2.0 mo (95% CI, 1.9–2.1). 12-mo OS rate was 32.7%. In KN028, ORR was 13.0% (3/23, all PR; 95% CI, 2.8%–33.6%) and median DOR was NR (range, 21.5 to 29.4+ mo). Median OS and PFS were 6.2 mo (95% CI, 3.8–10.3) and 1.8 mo (95% CI, 1.4–3.7), respectively. 12-mo OS rate was 27.6%. Grade 3–5 treatment-related AEs occurred in 13.5% in KN158 (1 pt had grade 5 renal failure) and 16.7% of pts in KN028 (no grade 5). 18.3% in KN158 and 20.8% of pts in KN028 had an immune-mediated AE or infusion reaction.

Conclusions: Pembro provides durable antitumor activity, regardless of PD-L1 expression, and manageable toxicity in a subset of pts with advanced BTC. Clinical trial information: NCT02054806 and NCT02628067

Lenvatinib (len) plus pembrolizumab (pembro) for the 1L treatment of patients (pts) with advanced HCC: Phase 3 LEAP-002 study.

Abstract No: TPS4152

Background: Len, an inhibitor of VEGF receptors 1-3, FGF receptors 1-4, PDGF receptor α, RET, and KIT, is approved for first-line treatment of unresectable HCC (uHCC) based on the open-label phase 3 REFLECT study in which len showed noninferior overall survival (OS) and significantly improved objective response rate (ORR), progression-free survival (PFS), and time-to-progression (TTP) vs sorafenib. In the phase 2 KEYNOTE-224 study of pembro (a PD-1 inhibitor) as second-line treatment of advanced HCC, pembro showed meaningful clinical efficacy in pts previously treated with sorafenib, with median PFS 4.9 mo, median OS 12.9 mo, and a manageable safety profile. In results from the phase 1b KEYNOTE-524 trial, len+pembro was well-tolerated, with promising antitumor activity in pts with uHCC.
LEAP-002 is a phase 3 study to evaluate the safety and efficacy of len+pembro vs len+placebo as first-line therapy for advanced HCC.

Methods: Eligible pts are ≥18 y and have HCC confirmed by radiology, histology, or cytology; ECOG PS 0/1; BCLC stage C or stage B disease not amenable to locoregional therapy or curative treatment approach; CP class A liver score within 7 days before study; and ≥1 measurable lesion by RECIST v1.1. Pts with past or ongoing HCV infection and those with controlled HBV are eligible. 750 pts will be randomized 1:1 to receive len 12 mg (body weight [BW] ≥60 kg) or 8 mg (BW <60 kg) orally once daily plus pembro 200 mg or placebo IV Q3W. Pembro and len will be administered until disease progression or unacceptable toxicity, with a maximum 35 cycles for pembro. Stratification will be by geographic region (Asia vs Japan and Western regions); macroscopic portal vein invasion or extrahepatic spread or both (yes or no); alpha fetoprotein ≤400 ng/mL vs >400 ng/mL; and ECOG PS 0/1. Primary end points are PFS per RECIST v1.1 by blinded independent central review (BICR) and OS. Secondary end points are ORR, duration of response, disease control rate, and TTP per RECIST v1.1 by BICR, efficacy per modified RECIST, pharmacokinetics, and safety. Imaging assessments will be performed Q9W on study. AEs will be graded per CTCAE v4.0 and monitored up to 90 days after last dose. Clinical trial information: NCT03713593

Phase 3 (COSMIC-312) study of cabozantinib (C) in combination with atezolizumab (A) versus sorafenib (S) in patients (pts) with aHCC who have not received previous systemic anticancer therapy.

Abstract No: TPS4157

Background: C inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (Tyro3, AXL, MER). C is approved for treatment of aHCC after prior S based on improved overall survival (OS) vs placebo in the phase 3 CELESTIAL trial (Abou-Alfa NEJM 2018). Standard of care for first-line treatment of aHCC is tyrosine kinase inhibition with S or lenvatinib, and phase 3 trials of immune checkpoint inhibitors (ICIs) in first- and second-line aHCC are ongoing. C may promote an immune-permissive tumor environment, which could enhance response to ICIs. C is being evaluated in combination with the anti-PD-L1 antibody A in multiple tumor types including HCC in a phase 1 study; and dose, preliminary clinical activity, and safety have been established in aRCC (Agarwal Ann Oncol 2018). A in combination with bevacizumab, an anti-VEGF antibody, has shown preliminary clinical activity in first-line aHCC (Pishvaian Ann Oncol 2018). Here, we present the study design of a phase 3 trial of C+A vs S as first-line treatment for aHCC who have not received prior systemic therapy.

Methods: This international, randomized, open-label phase 3 trial (NCT03755791) is evaluating the efficacy and safety of C+A vs S as first-line treatment for aHCC. Eligibility criteria include age ≥18 years, BCLC stage B or C, Child-Pugh A, ECOG PS 0 or 1, and measurable disease per RECIST 1.1. Patients are randomized 6:3:1 to an experimental arm of C (40 mg qd) + A (1200 mg infusion q3w), a control arm of S (400 mg bid), and an exploratory arm of C monotherapy (60 mg qd). 640 pts are planned at ~200 sites globally. Randomization is stratified by disease etiology (HBV [with or without HCV], HCV [without HBV], or other), region (Asia, other), and the presence of extrahepatic disease and/or macrovascular invasion (yes, no). OS and progression-free survival are coprimary endpoints and objective response rate is a secondary endpoint. Additional endpoints include safety, pharmacokinetics, and correlation of biomarker analyses with clinical outcomes. Enrollment in COSMIC-312 is ongoing. Clinical trial information: NCT03755791

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First-line avelumab + axitinib in patients with advanced hepatocellular carcinoma: Results from a phase 1b trial (VEGF Liver 100).

Abstract No: 4072

**Background:** Combining an immune checkpoint inhibitor with a targeted antiangiogenic agent may leverage complementary mechanisms of action for treatment of advanced/metastatic (a/m) hepatocellular carcinoma (HCC). Avelumab is a human anti-PD-L1 IgG1 antibody with clinical activity in various tumor types; axitinib is a tyrosine kinase inhibitor selective for VEGF receptors 1/2/3. VEGF Liver 100 (NCT03289533) is a phase 1b study evaluating safety and efficacy of avelumab + axitinib in treatment-naive patients (pts) with HCC; interim results are reported here.

**Methods:** Eligible pts had confirmed a/m HCC, ≥1 measurable lesion, a fresh or archival tumor specimen, ECOG PS ≤1, and Child-Pugh class A. Pts received avelumab 10 mg/kg IV Q2W + axitinib 5 mg orally BID until progression, unacceptable toxicity, or withdrawal. Endpoints included safety and objective response (RECIST v1.1; modified [m] RECIST for HCC).

**Results:** Interim assessment was performed after a minimum follow up of 6 months based on the released study data set (clinical cut-off date: Aug 1, 2018). As of the cut-off date, 22 pts (median age: 68.5 y) were treated with avelumab (median: 20.0 wk) and axitinib (median: 19.9 wk). The most common grade 3 treatment-related adverse events (TRAEs) (≥10% of patients) were hypertension (50.0%) and hand-foot syndrome (22.7%); no grade 4/5 TRAEs were reported. Immune-related AEs (irAEs) (≥10% of pts) were hypothyroidism (31.8%) and hyperthyroidism (13.6%). No grade ≥3 irAEs were reported; no pts discontinued treatment due to TRAEs or irAEs. Based on Waterfall plot calculations, tumor shrinkage was observed in 15 (68.2%) and 16 (72.7%) pts by RECIST and mRECIST, respectively. ORR was 13.6% (95% CI, 2.9%-34.9%) and 31.8% (95% CI, 13.9%-54.9%) by RECIST and mRECIST, respectively. OS data were immature at data cutoff.

**Conclusions:** The preliminary safety of avelumab + axitinib in HCC is manageable and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies. This study demonstrates antitumor activity of the combination in HCC. Follow-up is ongoing. Clinical trial information: NCT03289533


Abstract No: 4082

**Background:** For patients with advanced BTC, standard chemotherapy has limited benefit and no molecular targeted agents have been approved. Pembrolizumab is an anti PD-1 immune checkpoint inhibitor which has shown modest activity for advanced BTC patients in prior single-arm phase I/II studies. Considering the heterogeneity of BTC, more data are needed to evaluate the clinical outcomes of pembrolizumab in unresectable or metastatic BTC.

**Methods:** In this prospective cohort study, 39 patients with PD-L1 positive BTC who received pembrolizumab in Asan Medical Center, Seoul, Korea were included (ClinicalTrials.gov identifier, NCT03695952). PD-L1 expression was assessed using immunohistochemistry and PD-L1 positive tumors were defined as the expression of PD-L1 in ≥ 1% of tumor cells. Pembrolizumab was given at a fixed dose of 200 mg intravenously, every 3 weeks.
**Results:** The median age was 61 years old (range, 41-76) and 22 (56.4%) patients were male. Intrahepatic cholangiocarcinoma (CCA) was the most common type (n = 18, 46.2%), followed by gallbladder cancer (n = 12, 30.8%) and extrahepatic CCA (n = 9, 23.1%). Most of the patients had distant metastasis (n = 37, 94.9%). Pembrolizumab was administered as 2nd-, 3rd- and 4th or greater line chemotherapy in 18 (46.2%), 16 (41.0%) and 5 (12.8%) patients, respectively, and median 2 cycles (range 1-10) of pembrolizumab were given. In 36 patients whose response was assessable, partial response (PR) and stable disease were achieved in 4 (11.1%) and 13 (36.1%), respectively. In 19 (52.8%) patients, progressive disease was the best response. In patients with PR, the median time to response was 2.1 months (95% confidence interval (CI), 0.4 – 3.9). With a median follow-up duration of 4.4 months (95% CI, 2.4 – 6.4), median progression-free survival and overall survival was 1.5 months (95% CI, 0.4 – 2.6) and 4.3 months (95% CI, 2.6 – 6.1), respectively. No grade 3/4 adverse events (AEs) were reported and grade 1/2 fatigue (n = 4, 10.3%) was the most common AE.

**Conclusions:** In PD-L1 positive BTC, pembrolizumab showed modest efficacy with 11.1% of response rates although our patients were heavily pretreated. Considering the limited therapeutic options and poor survival for these patients, further evaluation of immunotherapy including biomarker analysis is needed.

**A phase II study of nivolumab in patients with advanced refractory biliary tract cancers (BTC).**

**Abstract No:** 4097

**Background:** Biliary tract cancers (BTC) are often typically diagnosed at an advanced stage. There is no established second line option for patients with advanced BTC who have failed one prior systemic therapy. The phase II study evaluated safety and efficacy of nivolumab, anti PD-1 antibody in refractory BTC patients.

**Methods:** Pts with histologically proven BTC who progressed on at least one line but no more than three lines of systemic therapy received nivolumab 240mg IV q2weeks for 16 weeks and then 480 mg IV every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint of the study was objective response rate (ORR) by RECIST 1.1 every 8 weeks. The Simon two staged design was used to assess ORR. 18 patients were accrued and if one response was seen, the plan was to accrue additional 34 patients. Secondary endpoints were PFS, OS and safety profile.

**Results:** At data cutoff (Jan 14, 2018), 54 patients with BTC (female: 50%, Median age: 65 years) were enrolled. The primary sites of tumor were intrahepatic cholangiocarcinoma (63%) extrahepatic (11%), and gallbladder (26%). 30 pts (56%) failed 1 line of therapy and 24 (44%) failed more than one line of therapy. 45 pts (1 pt withdrew consent, 1pt just enrolled prior to data cutoff and 7 pts came off the study due to clinical progression) were evaluable for response rate. Out of 45 pts, 10 pts (22%) achieved PR (1 unconfirmed PR) and 17 pts (37.8%) achieved SD. DCR was 60%. All patients who responded were microsatellite stable. For evaluable 45 pts with median follow up of 13.34 months, median PFS was 3.98 months (95% CI: 2.33-5.98) and the median OS was 14.22 months (95% CI: 6.64-NA). 6 and 12-month OS was 71.4 and 52.3% and 6 and 12-month PFS was 35.2% and 24.1% respectively. Most common treatment related AEs (TRAE) was alkaline phosphatase increased (24.5%). Grade III/IV TRAEs were seen in 11 pts (20.4%); most common were hyponatremia (3 pts) and elevated alkaline phosphatase (2 pts). No treatment related AEs led to discontinuation of the study drug. Tissue samples were collected in all pts with planned correlative studies underway including the PDL 1 status.

**Conclusions:** Nivolumab was well tolerated and has shown promising efficacy in refractory BTC including durable responses lasting 2 years. Further randomized trial is warranted in refractory BTC. Clinical trial information: NCT02829918
Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040.

Abstract No: 4012

**Background:** NIVO monotherapy (mono) is approved for sorafenib (SOR)-treated pts with HCC based on data from CheckMate 040 (NCT01658878), which reported an objective response rate (ORR) of 14% and median overall survival (mOS) of 16 months (mo). This is the first report of efficacy and safety of the NIVO + IPI combination in SOR-treated pts with aHCC.

**Methods:** Pts were randomized to 3 arms: [A] NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) or [B] NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W, or [C] NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W. Treatment continued until intolerable toxicity or disease progression. Primary endpoints included safety and tolerability. Secondary endpoints included ORR (BICR per RECIST v1.1), duration of response (DOR), disease control rate (DCR), and OS. Cutoff was 25 Sep 2018.

**Results:** 148 SOR-treated pts were randomized. Minimum follow-up for OS from last pt randomization date to data cutoff was 24 mo. At baseline: 88% had vascular invasion or extrahepatic spread, 91% had BCLC stage C, 84% discontinued SOR due to disease progression and 14% due to toxicity. Overall, ORR was 31% (7 had a complete response [CR]) with a median DOR of 17 mo; DCR was 49% and 24-mo OS rate was 40%. Pts in arm A had a mOS of 23 mo and 4 pts had a CR. The table shows additional efficacy results by arm. Overall, NIVO + IPI was well tolerated; 37% of pts had a grade 3–4 treatment-related adverse event (TRAE; most common: pruritus and rash); 5% had grade 3–4 TRAEs leading to discontinuation.

**Conclusions:** NIVO + IPI led to clinically meaningful responses and had an acceptable safety profile in SOR-treated pts, with an ORR twice that of NIVO mono (31% and 14%, respectively). Pts in arm A had the most promising mOS of 23 mo. Clinical trial information: [NCT01658878](https://clinicaltrials.gov/show/NCT01658878)

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Derazantinib (DZB) provides antitumor efficacy regardless of line of therapy in patients (pts) with FGFR2-fusion positive advanced intrahepatic cholangiocarcinoma (iCCA).

Abstract No: e15607

**Background:** FGFR2 fusions are prevalent in 13-22% of iCCA and known oncogenic drivers. DZB is a kinase inhibitor with potent pan-FGFR activity. In a non-comparative Phase 2a study, DZB was administered to 29 pts with FGFR2-fusion positive advanced, inoperable iCCA, either as first-line (1L) (n = 2), 2L (n = 13), 3L (n = 10), 4L (n = 2) or 5L therapy (n = 2). The objective response rate (ORR) with DZB was 21%, disease-control rate (DCR) 83% and median PFS 5.7 months (Mazzaferro et al. 2018 BJC). Data from biliary tract cancer studies suggest decreasing treatment effects of chemotherapy with increasing lines of treatment. Here, we present a post-hoc analysis of outcomes of pts treated with DZB in 1L/2L (n = 15) compared to pts treated post-2L (n = 14).
Methods: Pts received 300 mg DZB QD PO. Eligibility criteria included locally confirmed, positive testing of FGFR2 fusion expression (FISH or NGS), ECOG PS 0-1. Objective responses were determined using RECIST 1.1. Disease control rate was defined as CR, PR or SD.

Results: The mean age of pts treated in 1L/2L was 66y and 55y in post-2L; 73% were females in 1L/2L and 50% in post-2L treatment; other demographic variables were balanced between groups (87% vs 86% of liver target lesions, median baseline lesion size of 97.5 mm vs 109.5 mm, ECOG PS0 was 60% vs 71%). Of 15 1L/2L group pts, 12 (80%) had prior platinum-based chemotherapy as compared to all 14 pts in the post-2L group. In the 1L/2L and post-2L groups, ORR was 20% and 21%, DCR was 80% and 86%, and a reduction in sum of the largest diameter of target lesions was observed in 60% and 64% of pts, respectively. Median PFS was 5.5 mo (95% CI, 1.9-11.9) and 6.2 mo (3.6-9.2) for the 1L/2L and post-2L groups, respectively. Types of drug-related adverse events were similar in 1L/2L and post-2L.

Conclusions: Anti-tumor efficacy of DZB in iCCA patients measured either by ORR, DCR, tumor shrinkage or PFS was numerically similar irrespective of treatment line. These data suggest that DZB is an effective treatment option that can be applied early in the treatment continuum of iCCA patients or at later stages to offer anti-tumor efficacy and disease control. Clinical trial information: 01752920.

A phase I study of H3B-6527 in HCC or intrahepatic cholangiocarcinoma (ICC) patients (pts).

Abstract No: 4095

Background: FGF19 overexpression is hypothesized to hyperactivate FGFR4 and its downstream signaling pathway leading to enhanced tumor growth in HCC/ICC. Targeting FGFR4 may have therapeutic benefit in HCC/ICC with altered FGF19 signaling. A phase 1 study (NCT02834780) was initiated to assess H3B-6527, an investigational highly selective covalent FGFR4 inhibitor.

Methods: Adult pts with advanced HCC or ICC, ECOG PS 0-1, well compensated liver function, and who progressed after at least one prior therapy, were administered H3B-6527 orally QD (once daily) on a 21-day cycle following a 3+3 design. Patients in the dose escalation phase were treated regardless of FGF19 status. Adverse events (AEs), pharmacokinetics (PK), and pharmacodynamics (PD) were assessed. Response was determined by RECIST 1.1 or modified RECIST every 6 weeks.

Results: As of 06-Jan-2019, 37 pts have been treated with H3B-6527 at doses of 300 to 1400 mg QD (23 pts in escalation; 14 in expansion). In dose escalation, a total of 17 patients with HCC, Child-Pugh A received prior systemic therapy including 100% with prior TKI and 35% with prior IO. 12% had hepatitis B virus and 47% had hepatitis C virus. H3B-6527 plasma levels increased with dose from 300 to 1000 mg QD and plateaued. H3B-6527 was rapidly absorbed with a $t_{\text{max}}$ of ~2-3 h and showed a terminal half-life of ~4-5 h, following administration of 1000 mg (fasted). No dose-limiting toxicities or ≥ Grade 3 treatment-related AEs (TRAE) have been observed in escalation. Most common TRAEs (≥ 10%) were diarrhea, nausea, and vomiting. Based on safety, PK, and PD, 1000 mg QD was the recommended phase 2 dose. Durable stable disease and partial responses (PR) have been observed on the once daily fasted schedule; 2 of 17 pts with HCC achieved PRs and an additional 7 with stable disease were on treatment for ≥ 5 months.

Conclusions: H3B-6527 is well tolerated and demonstrates early signs of clinical activity. Dose expansion on QD schedule and exploration of BID (twice daily) schedule is ongoing. Clinical trial information: NCT02834780
A phase II study of anti–PD-1 antibody camrelizumab plus FOLFOX4 or GEMOX systemic chemotherapy as 1L therapy for adv. HCC or biliary tract cancer.

Abstract No: 4074

**Background:** Advanced hepatocellular carcinoma (HCC) and biliary tract cancer (BTC) patients (pts) have very limited treatment options. Considering the immunogenic effects of oxaliplatin, combination of camrelizumab with oxaliplatin-based chemotherapy might bring a better clinical benefit.

**Methods:** That was an ongoing single-arm, multicenter phase 2 trial. Advanced HCC or BTC pts naive to systemic treatment were given camrelizumab (3 mg/kg i.v., every 2 weeks) plus typical FOLFOX4 (infusional fluorouracil, leucovorin and oxaliplatin) or GEMOX (gemcitabine and oxaliplatin) regimen. Primary endpoints were confirmed objective response rate (ORR) per RECIST v1.1 and safety per CTC AE 4.03.

**Results:** From Apr 27, 2017 to Oct 31, 2018, 34 Chinese HCC and 47 BTC pts were treated, in which 27 (79.4%) HCC and 17 (36.2%) BTC pts were HBV-infected. In the 34 evaluable HCC pts, confirmed ORR was 26.5% and disease control rate (DCR) was 79.4%. Median time to response (TTR) was 2.0 mo (range 1.5–5.7). Six of the 9 responses were still ongoing, and median duration of response (DoR) was not reached (range 3.3–11.5 mo). Median progression-free survival (PFS) was 5.5 mo. At data cutoff, 61.7% BTC pts were still receiving study drug. In the 43 evaluable BTC pts, with a median duration of exposure of 2.9 mo, confirmed ORR was 7.0% and DCR was 67.4%. Median TTR was 1.9 mo (range 1.8–2.1). Median DoR was 5.3 mo (range 3.7–7.0). Median PFS was not reached yet. Median estimates for overall survival in both HCC and BTC were also not reached. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 85.3% of HCC and 57.4% of BTC pts, most commonly neutrophil count decreased (HCC: 55.9%; BTC: 29.8%), white blood cell decreased (HCC: 38.2%; BTC: 21.3%), platelet count decreased (HCC: 17.6%; BTC: 12.8%), and anaphylaxis (BTC: 19.1%). Only one BTC pt stopped treatment due to a TRAE (recurrent Grade 2 anemia related to FOLFOX4). Grade ≥3 immune-related AEs occurred only in 5.9% of HCC (lipase increased) and 3.8% of BTC pts (anaphylaxis).

**Conclusions:** Camrelizumab plus FOLFOX4 or GEMOX chemotherapy was tolerable and might offer a new promising 1L choice for advanced HCC and BTC pts. Clinical trial information: **NCT03092895**

A multicenter phase II trial of rucaparib-nivolumab combination as maintenance therapy for patients with advanced biliary tract cancer.

Abstract No: TPS4153

**Background:** Patients (pts) with advanced biliary tract cancers (BTC) have a poor prognosis with a median overall survival (OS) less than 12 months. Using whole exome NGS, 26 (49%) pts in a 53 pt cohort had either DNA damage repair (DDR) pathway mutations (somatic and/or germline, n = 18), or isocitrate dehydrogenase 1 (IDH1) mutations (n = 8) and may have potentially benefited from PARP inhibition. Further, disruption of the mutated DDR pathways with a PARP inhibitor may result in increased mutational burden and neoantigens leading to immunogenicity, thus providing...
the rationale for combination with a PD-1 antibody. This phase 2 trial is designed to investigate the role of a PARP inhibitor in combination with a PD-1 antibody in pts with advanced BTC.

**Methods:** Key eligibility criteria include histologically confirmed advanced, unresectable biliary adenocarcinoma (intra- or extra-hepatic, and gallbladder) without progression after 4-6 months of 1st line platinum-based systemic chemotherapy, measurable disease per RECIST v1.1, ECOG PS 0-1, Child-Pugh A or B7, and absence of autoimmune disease or chronic steroid use. Primary objective is to evaluate progression-free survival (PFS) rate at 4 months. Secondary objectives include evaluation of objective response rate per immune related (ir)RECIST criteria, median PFS and OS, and safety in this patient population. Exploratory objectives include identification of predictive biomarkers of response and mechanisms of resistance through serial biopsies and blood collection (pre, on and post therapy), including sequential whole exome/transcriptomic analysis with immune cell subset analysis. Treatment includes rucaparib 600 mg PO BID on days 1-28 with nivolumab 240 mg on days 1, 15 Q4 weeks. In absence of disease progression, pts may continue therapy up to 2 years. Accrual goal is 32 evaluable pts. Using a null hypothesis value of a 63% PFS rate at 4 months, and an 85% alternative hypothesis, this ongoing study has 80% power, with a one-sided alpha of 0.05 to identify treatment efficacy in the study arm. Clinical trial information: NCT03639935

**Nab-paclitaxel plus S-1 as first line treatment for advanced or metastatic biliary tract adenocarcinoma: A phase 2 study.**

**Abstract**

**Background:** Gemcitabine plus cisplatin or S-1 can be used as first-line treatment for advanced or metastatic biliary tract adenocarcinoma. Multiple phase 2 studies found that gemcitabine, oxaliplatin, capecitabine, S-1 were not superior to gemcitabine plus cisplatin. Nab-paclitaxel plus S-1 was effective and well-tolerated in pancreatic cancer.

**Methods:** Patients with pathological confirmed advanced or metastatic biliary tract adenocarcinoma (gallbladder carcinoma, intrahepatic cholangiocarcinoma ICC, extrahepatic cholangiocarcinoma ECC) were treated with Nab-paclitaxel plus S-1 (Nab-paclitaxel 120mg/m², d1 and d8; S-1 80-120mg/d, d1-14; q21d). Patients that received PR or SD (RECIST1.1) after 6 cycles were given S-1 maintenance treatment. The primary endpoint was ORR. The study used Simon’s Two Stage design.

**Results:** From March 2016 to September 2018, we recruited 54 patients, with 27 males (50%). The median age was 58(34-73yrs). As of Dec 31 2018, the median treatment cycle was 4(1-6 cycles). 51 patients were evaluable for efficacy: PR 14(27.5%), SD 22 (DCR=PR+SD: 70.6%), PD 15 (29.4%). The median PFS was 6 months, and the median OS was 13.2 months. The response rate varied in different tumor location: gallbladder carcinoma 53.8% (7/13), ICC 18.2% (6/33), ECC 20% (1/5).Common grade 3/4 AEs were: leucopenia 17 (31.5%), hyperbilirubinemia 5(9.3%), Mucositis 4 (7.4%), neurotoxicity 2 (3.7%), diarrhea 2 (3.7%), omit 1(1.9%), fatigue 1 (1.9%), thrombocytopenia 1 (1.9%), ALT increase 1 (1.9%).

**Conclusions:** Nab-paclitaxel plus S-1 as first line treatment for advanced or metastatic biliary tract adenocarcinoma was effective and well-tolerated, especially for gallbladder carcinoma (ORR 53.8%). This regimen need further exploration. Clinical trial information: NCT03830606

**A multi-center phase Ib/II study of nal-irinotecan, 5-fluouracil and leucovorin in combination with nivolumab as 2L therapy for patients with advanced unresectable biliary tract cancer.**

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Abstract No: TPS4154

**Background:** Patients (pts) with advanced biliary tract cancers (BTC) have poor prognosis despite systemic chemotherapy, and treatment beyond first-line platinum doublet remains investigational. The immunomodulatory properties of conventional cytotoxic therapy, particularly in regard to the upregulation of PD-L1 expression rendering tumor cells more sensitive to T cell-mediated lysis and neoantigen production, rapid emergence of chemotherapy resistance, and known modest efficacy of single agent PD-1 antibody in BTC provide a rationale for combining chemotherapy and immunotherapy. This multi-center, phase Ib/II, single-arm study is designed to investigate the role of nal-inotocan, 5-FU and leucovorin in combination with nivolumab as second-line therapy in pts with advanced BTC.

**Methods:** Key eligibility criteria include histologically confirmed advanced, unresectable biliary carcinoma (intra- or extra-hepatic and gallbladder) with progression or intolerance of first-line systemic therapy (excluding irinotecan and PD-1/PD-L1 antibody), measurable disease per RECIST v1.1, ECOG PS 0-1, Child Pugh A or B7, and absence of autoimmune disease or chronic steroid use. Primary objective of the phase Ib portion is to determine the recommended phase 2 dose, and of the phase II portion is to evaluate the median progression-free survival. Secondary objectives include evaluation of objective response rate per immune related (ir)RECIST, median OS and safety in this patient population. Exploratory objectives include identification of biomarker predictors of response and mechanisms of resistance through serial biopsies and blood collection (pre, on and post therapy), including sequential whole exome/transcriptomic analysis and immune cell subset analysis (tissue and blood). Therapy includes nal-inotocan 70 mg/m², leucovorin 200 (dose level -1) or 400 mg/m² (dose level 0), 5-fluouracil 2400 mg/m² IV over 46 hours, and nivolumab 240 mg on day 1 every 2 weeks for 6 months. In the absence of disease progression, pts may continue therapy for up to 2 years. Accrual goal is 30 evaluable pts. Using a null hypothesis value of median PFS of 2.9 months, and an alternative hypothesis of 5.0 months, this ongoing study has > 80% power, with a two-sided alpha of 0.05 to identify treatment efficacy of study arm. Clinical trial information: NCT03785873

**ABC-06 | A randomized phase III, multi-center, open-label study of Active Symptom Control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously treated with cisplatin/gemcitabine (CisGem) chemotherapy.**

Abstract No: 4003

**Background:** Level A evidence supports use of CisGem as first-line chemotherapy for ABC; no robust evidence is available for second-line chemotherapy.
Methods: Pts diagnosed with ABC with disease progression after prior CisGem were randomised (1:1) to either ASC+mFOLFOX or ASC. Randomisation was stratified by serum albumin levels (< 35 vs ≥35 g/L), platinum sensitivity (determined from first line CisGem) and disease extent (locally advanced vs metastatic). Pts with ECOG PS0-1, adequate haematological, renal and liver function, and adequate biliary drainage were eligible. Primary end-point was overall survival (OS) (multivariable Cox regression adjusted for stratification factors); sample size: 162 pts delivering 148 events were required (80% power; 5% two-sided alpha) for a hypothesised hazard ratio (HR) of 0.63. Assumed median survival for ASC was 4 months.

Results: 162 pts (81 in each arm) were randomized (27 March ‘14 - 04 Jan ‘18); median age 65 yrs (range 26-84); sex: 80 (49%) male, 82 (51%) female; primary site: intrahepatic 72 (44%), extrahepatic 45 (28%), gallbladder 34 (21%) and ampullary 11 (7%). Baseline characteristics were balanced between arms except platinum sensitivity (ASC+mFOLFOX 27 pts (33%); ASC 34 pts (42%)). After 150 OS events, the adjusted HR was 0.69 (95% CI 0.50-0.97; p = 0.031; ASC+mFOLFOX vs ASC). Median OS (months (m)), 6m and 12m OS-rate (%) were 6.2m, 50.6% and 25.9% for the ASC+mFOLFOX and 5.3m, 35.5%, 11.4% for the ASC arm, respectively. Grade 3/4 toxicities were reported in 48 (59%) and 32 (39%) pts in the ASC+mFOLFOX and ASC arm, respectively; these were balanced between arms except for fatigue and neutropenia (more frequent in ASC+mFOLFOX arm); data cleaning is ongoing. No chemotherapy-related deaths were reported.

Conclusion: Survival with ASC was greater than assumed; ASC+mFOLFOX improved OS after progression to CisGem with a clinically meaningful increase in 6m and 12m OS rate. ASC+mFOLFOX should become standard of care in second-line for ABC. Clinical trial information: NCT01926236

APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma.

Abstract No: 4000

Background: In metastatic pancreatic cancer (PC), nab-P/G demonstrated significantly longer overall survival (OS) vs G. APACT assessed efficacy & safety of nab-P/G vs G in surgically resected PC.

Methods: Treatment (tx)-naive patients (pts) with histologically confirmed PC, macroscopic complete resection, ECOG PS 0/1, & CA19-9 < 100 U/mL were eligible. Stratification factors: resection status (R0/R1), lymph node status (LN+/-), & geographic region. Tx was initiated ≤ 12 wks postsurgery. Pts received nab-P 125 mg/m² + G 1000 mg/m² or G 1000 mg/m² on days 1, 8, 15 of six 28-day cycles. Primary endpoint was disease-free survival (DFS) by independent reviewer (IR); IRs received baseline clinical data & scans. Secondary endpoints were OS & safety. ~438 DFS events were needed for 90% power to detect an HR for disease recurrence or death of 0.73 with nab-P/G vs G at a 2-sided significance level of 0.05.
**Results:** 866 pts were randomized. Median age was 64 y (range, 34 - 86); most pts had ECOG PS 0 (60%), LN+ (72%), & R0 (76%). 69% of pts completed 6 tx cycles (nab-P/G, 66%; G, 71%). Median follow up for OS was 38.5 mo. Median IR-assessed DFS (439 events) was 19.4 mo (nab-P/G) vs 18.8 mo (G) (HR, 0.88; 95% CI, 0.729 - 1.063; stratified log-rank P = 0.1824). Investigator-assessed DFS (571 events) was 16.6 mo (nab-P/G) vs 13.7 mo (G) (HR, 0.82; 95% CI, 0.694 - 0.965; nominal P = 0.0168). Interim OS (427 events) was 40.5 mo (nab-P/G) vs 36.2 mo (G) (HR, 0.82; 95% CI, 0.680 - 0.996; nominal P = 0.045). Grade ≥ 3 TEAEs were reported in 86% vs 68% of pts with nab-P/G vs G. The most common grade ≥ 3 hematologic & nonhematologic TEAEs with nab-P/G vs G were neutropenia (49% vs 43%) & fatigue (10% vs 3%). TEAEs led to death in 2 pts in each arm.

**Conclusions:** IR DFS with nab-P/G was not significantly longer vs G; median DFS with G was longer than historical data. DFS by investigator (sensitivity analysis) and interim OS were improved with nab-P/G vs G (HR 0.82 for both). Adjuvant nab-P/G may be an option for pts who are ineligible for FOLFIRINOX. Additional OS follow-up may better support nab-P/G as an option in the adjuvant setting. Clinical trial information: NCT01964430

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**Frequency of BRCA mutation in biliary tract cancer and its correlation with tumor mutational burden (TMB) and microsatellite instability (MSI).**

**Abstract No:** 4085

**Background:** Biliary tract cancers constitute ~3% of cancers worldwide with incidence increasing, especially for intrahepatic cholangiocarcinoma (IHC). The prognosis of these tumors remains dismal and novel treatment strategies are needed to improve overall survival. BRCA mutations occur in biliary tract cancers but their frequency in distinct sites of biliary tract cancer is unknown. Moreover, no data are available correlating BRCA mutation with immunogenic markers such as TMB, MSI, or PD-L1 expression.

**Methods:** Tumor samples from 1288 primary biliary tract cancers, comprising IHC (n = 746), extrahepatic cholangiocarcinoma (EHC) (n = 189), gallbladder (GBC) (n=353) were profiled at Caris Life Sciences, Phoenix, AZ. Testing included NextGen SEQ (MiSeq on 47 genes, NextSeq on 592 genes) and PD-L1 IHC (SP142). TMB was calculated based on somatic nonsynonymous missense mutations, and MSI was evaluated by NGS of known MSI loci.

**Results:** BRCA mutations were detected in 3.6% (N = 46) of samples (BRCA1 0.6%, BRCA2 3%), no differences were seen based on the site of the tumor. In GBC and IHC BRCA2 mutations (4.0% and 2.7%) were more frequent than BRCA1 (0.3% and 0.4, p < 0.05) while in EHC, similar frequency was observed (BRCA1: 2.1%; BRCA2: 2.6%). There was no significant association with gender or age. In BRCA-mutant biliary tract cancer the most frequently mutated genes were TP53 (55.6%), ARID1A (52.2%) and KRAS (26.1%), KMT2D/C (20%, 13%) and CDKN2A(13%). Overall, BRCA mutations were associated with a higher rate of MSI-H (19.5% vs 1.7%, p = 0.001) and higher TMB in both MSI-H and MSS tumors (p<0.05). When investigated separately, BRCA association with elevated TMB was seen in IHC and EHC, but not in GBC. No correlation was seen with PD-L1 expression. TP53, KMT2D/C, RB1, PTEN, KDM6A mutations and FGFR1 amplifications were significantly higher in BRCA mutated tumors (p < 0.05).

**Conclusions:** BRCA mutations are found in a significant subgroup of biliary tract tumors and are associated with an immunogenic tumor profile. These data provide rationale for trials testing PARP inhibitors in combination with immunotherapy and targeted therapies in patients with BRCA-mutant biliary tract cancers that are MSS.