PD-3 Phase 1 trial of vibostolimab plus pembrolizumab for PD-1/PD-L1 inhibitor-naive advanced gastric cancer: The KEYVIBE-001 trial

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Background: In the ongoing phase 1 KEYVIBE-001 trial (NCT02964013), the anti-TIGIT antibody vibostolimab+pembrolizumab showed promising antitumor activity in PD-1/PD-L1 inhibitor-naive NSCLC, ovarian cancer, and cervical cancer. We present the safety and efficacy of vibostolimab 200mg+pembrolizumab and vibostolimab 700mg+pembrolizumab in advanced gastric cancer (GC).

Methods: Patients had advanced PD-1/PD-L1 inhibitor-naive adenocarcinoma of the stomach and/or gastroesophageal junction measurable per RECIST v1.1 that progressed on $\geq$1 prior chemotherapy regimen or HER2-targeted therapy (in HER2-positive tumors). Patients with known mismatch repair-deficient and microsatellite instability-high (dMMR/MSI-H) tumors were excluded. In the dose-escalation phase, patients received either vibostolimab 200mg or 700mg, per the modified toxicity probability interval design, + pembrolizumab 200mg IV Q3W, given sequentially, for $\leq$35 cycles or until confirmed PD, unacceptable toxicity, or withdrawal from study. During the dose-confirmation phase, additional patients were treated at the recommended phase 2 dose of vibostolimab 200mg + pembrolizumab 200mg IV Q3W. Primary end points were safety and tolerability; AEs were assessed continually during treatment and for 90 days, or 30-90 days if new anticancer therapy was initiated, after treatment discontinuation using NCI CTCAE v4.0. The secondary end point was ORR per RECIST v1.1 by investigator review. Exploratory end points included DOR and PFS per RECIST v1.1 by investigator review. PD-L1 positivity was defined as combined positive score (CPS) $\geq$1 or when CPS was missing, as tumor proportion score $\geq$1% or as mononuclear immune cell density score $\geq$2.

Results: Of 27 patients with advanced GC enrolled, 24 received vibostolimab 200mg+pembrolizumab and 3 received vibostolimab 700mg+pembrolizumab. Median age was 63 years (range, 35-78); 59% of patients were male, 56% had an ECOG performance status of 0, and 59% were previously treated with $\geq$2 lines of therapy. Among all patients, 41% of tumors were PD-L1-positive and 7% were HER2-positive. Median follow-up was 12 months (range, 6-19). No dose-limiting toxicities occurred in the dose-escalation phase. Treatment-related AEs (TRAEs) occurred in 52% of patients; 15% had grade 3 or 4 TRAEs and no grade 5 events were reported. The most common TRAEs ($\geq$5%) were rash (19%), anemia (7%), hyperthyroidism (7%), and infusion-related reactions (7%). ORR was 11% (3/27; 3 PR) in all patients, 13% (3/24; 3 PR) with vibostolimab 200mg, and 0% (0/3) with vibostolimab 700mg. When evaluated by PD-L1 status, ORR was 27% (3/11; 3 PR) in PD-L1-positive and 0% (0/13) in PD-L1-negative tumors. Of 20 patients with PD-L1 CPS data, overall ORR was 15% (3/20; 3 PR); ORR was 33% (3/9; 3 PR) in patients with CPS $\geq$1 and 0% (0/11) in patients with CPS $<$ 1. Among responders, median DOR was 10 months (range, 6+ to 11); retrospective testing confirmed none of these tumors were MSI-H. Median PFS was 2 months (95% CI, 2-4).

Conclusions: In patients with advanced PD-1/PD-L1 inhibitor-naive GC, vibostolimab+pembrolizumab had a comparable safety profile to other cohorts that received the combination, and no new safety signals were identified. Promising antitumor activity was observed at the vibostolimab 200mg dose and in patients with PD-L1-positive tumors, warranting further investigation of vibostolimab 200mg and pembrolizumab in PD-L1-positive GC.

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PD-4 Genetic aberration from normal tissues adjacent to biliary tract cancers

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Background: Chronic inflammation has emerged as a main mediator of the adenoma-carcinoma sequence in the carcinogenesis of biliary tract cancers (BTCs). Therefore, normal tissues adjacent to the tumor (NATs) may harvor tumor-related genetic abberations due to chornic inflammation such as sclerosing cholangitis. The purpose of this study was to determine the differences of genetic alterations between BTCs and NATs in surgically resected specimen.

Methods: We describe successful NGS-based testing of 13 paired peripheral blood, NATs and BTCs from patients with 4 distal cholangiocarcinomas, 2 hilar cholangiocarcinomas, 3 intra- hepatic cholangiocarcinomas and 4 gallbladder cancers. Tissues from biliary tract cancers and normal tissues adjacent to the tumor were frozen in liquid nitrogen $<$ 30 min after surgery and stored at -80°C until the time of DNA extraction. DNA was purified using the QIAamp DNA Mini Kit (Qiagen). Whole genome and exome sequencing was performed using the illumina HiSeq 2000 sequencing platform.

Results: Genetic aberrations were more frequently founded in NATs than BTCs. Three hyper-mutated BTC samples shared more than 3000 genetic mutations (more than 90% of total genetic mutations) with NATs. But in cases of non-hypermutated tumor, only 23% of mutations were shared between BTC and NAT. NCOR2, MUC16, CHD4, PDE4DIP, ZFHX3, TP53, ARID1B, SMAD4, ELF3, RECQL4 and RBM10 were common BTCs-related genes. ANKRD36, IQCA1, PDE4DIP, COL6A6, TP53 and ARID1B appeared in both BTCs and NATs. ANKRD36:chr2:97163323: p.Arg301Thr was the most common mutation in NATs, but the correlation with ANKRD36 and BTCs are unknown until now.

Conclusions: We revealed several mutations may be valuable for detecting an early carcinogenesis, but further studies are needed.

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PD-5 IDH1 in intrahepatic cholangiocarcinoma: A comparative genomic analysis and clinical impact

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Background: IDH1-mutated cholangiocarcinomas (CCAs) are an interesting group of neoplasia with particular behavior and therapeutic implications. The aim of the present work is to highlight the differences characterizing IDH1m and IDH1wt CCAs in terms of genomic landscape.

Methods: 284 patients with iCCA treated for resectable, locally advanced or metastatic disease were selected and studied with the FOUNDATION Cdx technology. A comparative genomic analysis and survival analyses for the most relevant altered genes were performed between IDH1m and IDH1wt patients.

Results: Overall, 125 patients were IDH1m and 122 IDH1wt. IDH1m patients showed higher mutation rates compared to IDH1wt in CDKN2B and lower mutation rates in several genes including TP53, FGFR2, BRCA2, ATM, MAP3K1, NOTCH2, ZNF703, CCND1, NBN, NF1, MAP3KI3, and RAD21. At the survival analysis, IDH1m and IDH1wt

patients showed no statistically differences in terms of survival outcomes, but a trend in favor of IDH1wt patients was observed. Differences in prognostic values of the most common altered genes were reported. In surgical setting, in IDH1m group the presence of CDKN2A and CDKN2B mutations negatively impact DFS, whereas the presence of CDKN2A, CDKN2B, and PBRM1 mutations negatively impact OS. In advanced setting, in the IDH1m group, the presence of KRAS/NRAS and TP53 mutations negatively impact PFS, whereas the presence of TP53 and PIK3CA mutations negatively impact OS; in the IDH1wt group, only the presence of MTAP mutation negatively impact PFS, whereas the presence of TP53 mutation negatively impact OS.

Conclusions: We highlighted several molecular differences with distinct prognostic implications between IDH1m and IDH1wt patients.

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PD-6 DNA methylome as a potential biomarker in biliary brushes and bile fluid samples to differentiate between benign and malignant biliary stenosis

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Background: The diagnosis of perihilar and distal cholangiocarcinoma (CCA) remains an important clinical challenge. Current detection methods are mostly based on biliary brushing samples with suboptimal sensitivity and/or specificity, leading to late diagnosis and higher mortality rates.

Methods: We aimed to identify a diagnostic biomarker using targeted DNA methylation sequencing in a classical training and validation study-design. Biliary brushing and bile fluid samples from patients with known malignant versus benign biliary stenoses were prospectively collected during endoscopic retrograde cholangiopancreatography (ERCP). Clinical data including baseline patient characteristics and clinical follow-up data was recorded. All samples were subjected to targeted, enzymatic DNA methylation sequencing (EM-seq) using a total of 608,293 capture probes targeting genomic regions known to be hypermethylated in cancer. Differential methylation analysis was used to identify differentially methylated regions between benign and malignant samples. Only regions differentially methylated in both biliary brush and bile fluid samples were retained. These regions were used to train a 'random forest classification' based prediction model in a 'training cohort' of biliary brush samples, using 10-fold cross-validation. The remaining samples were then used as 'validation set' to test the potential of the methylation score in classifying malignant versus benign samples. Receiver operating characteristic curve analyses were used to evaluate the performance of both the brush-derived and bile fluid-derived methylation scores in differentiating malignant from benign samples.

Results: A total of 43 patients were included between November 2019 and September 2021. Twenty-eight patients had a known benign stenosis, the majority of which were due to ischemic cholangiopathy, while 15 patients had a known malignant stenosis due to CCA or pancreatic adenocarcinoma. Average capture coverage was significantly higher in brush-derived samples (59.6X versus 24.9X, respectively; $p < 0.001$). Differential methylation analysis between malignant and benign stenosis identified 669 genomic regions as differentially methylated in both sample types. Brush-derived methylation scores differentiated between malignant and benign with a specificity of 0.913 and sensitivity of 0.933 (AUC 0.93). Similarly, the methylation scores derived from bile fluid demonstrated a specificity of 0.961 and sensitivity of 0.8 (AUC 0.89).

Conclusions: We present a DNA-methylation based biomarker that accurately differentiates between malignant and benign biliary stenosis. Bile fluid aspiration during ERCP is a potential alternative when biliary brushing is not feasible. Further validation in larger cohorts is warranted.

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PD-7 Cabozantinib plus atezolizumab in previously untreated advanced hepatocellular carcinoma (aHCC) and previously treated gastric cancer (GC) and gastroesophageal junction adenocarcinoma (GEJ): Results of the COSMIC-021 study

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Background: Cabozantinib may enhance response to immune checkpoint inhibitors by promoting an immune-permissive microenvironment. COSMIC-021 (NCT03170960), a multinational phase 1b study, is evaluating cabozantinib plus atezolizumab in various solid tumors. Efficacy and safety results in previously untreated aHCC (cohort 14) and previously treated GEJ/GC (cohort 15) are presented.

Methods: Patients had measurable disease and ECOG PS of 0 or 1. Patients with aHCC, Child-Pugh A status, and no prior systemic anticancer therapy were eligible for cohort 14. Patients with GC, GEJ, or lower one-third esophageal adenocarcinoma who radiographically progressed during or following platinum- or fluoropyrimidine-containing chemotherapy and had $\leq$2 prior lines of therapy were eligible for cohort 15. Patients received cabozantinib 40 mg PO QD and atezolizumab 1200 mg IV Q3W. CT/MRI scans were performed Q6W for 52W and Q12W thereafter. The primary endpoint was ORR by investigator per RECIST 1.1. Other endpoints included safety, PFS, and OS.

Results: As of the data cutoff of 21 Dec 2021, 30 patients with aHCC and 31 with GEJ/GC (22 with GEJ, 8 with GC, and 1 other) were enrolled with a median (range) follow-up of 31.2 mo (23.0, 34.2) and 30.4 mo (19.5, 33.6), respectively. For aHCC, median age was 71 y, 12 (40%) had ECOG PS 0; disease etiology was 6 (20%) HBV, 11 (37%) HCV, and 13 (43%) non-viral. Extrahepatic invasion was present/absent in 13 (43%)/16 (53%), macrovascular invasion in 2 (7%)/20 (67%), and portal vein invasion in 10 (33%)/13 (43%). For GEJ/GC, median age was 61 y, 11 (35%) had ECOG PS 0, and 16 (52%), 14 (45%), and 1 (3%) received 1, 2, or 3 prior lines of systemic therapy. ORR per RECIST 1.1 was 13% (all confirmed PRs) for aHCC and 0 for GEJ/GC. Median DOR was 22.1 mo for aHCC. DCR (CR + PR + SD) was 83% for aHCC and 48% for GEJ/GC. Median PFS per RECIST 1.1 was 5.7 mo in aHCC and 2.4 mo in for GEJ/GC; median OS was 19.0 mo and 6.4 mo, respectively. Frequent treatment-related adverse events (TRAEs) for aHCC and GEJ/GC were PPE (47% and 13%), diarrhea (37% and 26%), AST increased (33% and 13%), and fatigue (23% both). Grade 3/4 TRAEs occurred in 40% for aHCC and 35% for GEJ/GC. No grade 5 TRAEs occurred in either cohort.

Conclusions: Cabozantinib plus atezolizumab had clinical activity with a manageable safety profile in previously untreated aHCC, consistent with the recently presented phase 3 results in this indication (NCT03755791). Clinical activity of cabozantinib plus atezolizumab was minimal in previously treated GEJ/GC.

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