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.

Clinical trial identification: NCT03170960.

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