the role of PC in BDC pathogenesis and progression. A therapeutic approach targeting OFD1 in BDC cells was also investigated.

Conclusions: We investigated the molecular mechanisms underlying the cilia loss and test whether may be potential therapeutic target. These findings could be useful to establish treatment and diagnostic strategies for BTCs based on genetic information.

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56P Serum protein signatures as potential novel diagnostic biomarkers for biliary tract cancer

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Background: Biliary tract cancer (BTC) has a very poor prognosis. The only potentially curative treatment is surgery, but most patients are ineligible for this treatment due to advanced disease. Thus, biomarkers that can identify BTC at an early stage are needed. We aimed to identify protein signatures that could discriminate patients with BTC from non-cancer participants.

Methods: The study included 191 patients with all stages of BTC (gall bladder cancer (n=37), intrahepatic cholangiocarcinoma (CC) (n=92), and extrahepatic CC (n=62), and 250 controls (healthy (n=90), benign biliary tract disease (n=25), and other benign diseases (n=135)). We analyzed serum levels of immuno-oncology (I-O) related proteins using the Olink I-O assay (Olink Proteomics, Sweden) as well as CA19-9. To identify protein signatures and test their performance, the cohort was split randomly in a training (2/3) and replication set (1/3). Signatures were identified in the training set using logistic elastic-net (Lasso and Ridge) regressions. We generated signatures with decreasing number of proteins based on the proteins' stability as predictors in Lasso regression. Signature performance was evaluated in both datasets using receiver operating characteristics (ROC) and area under the ROC curve (AUC). Sensitivity and specificity were calculated using best point.

Results: Sixteen unique protein signatures including 2 to 84 proteins were generated. All signatures included CA19-9 and chemokine (C-C motif) ligand 20 (CCL20). Overall, all signatures showed promising performance in both the training and replication set with AUC ranging from 0.95 — 0.99 for BTC vs. all controls. The lowest AUC was observed for signatures with less than 6 proteins. The best point sensitivity ranged from 91% -100% and specificity from 85% - 96% in the replication set. The best performing signatures achieved an AUC of 0.99 with a sensitivity of 96% and a specificity of 96%. All signatures identified patients with BTC independent of primary tumor location and stage (AUC $\geq$ 0.95).

Conclusions: We identified several protein signatures that could discriminate BTC patients from non-cancer participants with high sensitivity and specificity. A validation study in an independent cohort is ongoing.

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57P The characteristics of IDH mutations in Chinese bile duct carcinoma patients

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Background: The isocitrate dehydrogenase (IDH) is an important enzyme in the tricarboxylic acid cycle and IDH mutations play an important role in tumor treatment and prognosis evaluation. IDH mutations have been reported in approximately 15% of cholangiocarcinoma (CCA) patients, while these aberrations are considered to be less frequent in other bile duct carcinoma (BDC) patients. IDH inhibitors have been approved for targeted therapy, which holds great promise for improving the management of BDCs. Here we provide an overview of IDH mutations in a large cohort of Chinese BDCs.

Methods: BDC tissue specimens and/or circulating cell-free DNA from patients who had undergone molecular profiling were retrospectively reviewed. IDH1, IDH2 and other BDC related genes were detected using hybridization-based targeted next-generation sequencing.

Results: A total of 874 Chinese BDC cases had undergone molecular profiling from January 2017 to March 2021. We identified 60 IDH mutations in 59 of the 874 patients. Of these patients, Active-site mutations in IDH1 and IDH2 (IDH1_R132, IDH2_R140 and IDH2_R172) were detected in 50 patients (5.72%, 50/874), including 28 (56%) males and 22 (44%) females. The median age of patients with IDH active-site mutations was 57.5 years old (age range 32—79 years). Among the 60 IDH mutations, missense variation was the most frequent mutation category (98.3%, 59/60), and the other one was frameshift. Out of the 36 IDH1 active-site mutated specimens, 27 (75%) carried IDH1 R132C mutations, followed by IDH1-R132L (11.1%), IDH1-R132S (8.3%) and IDH1-R132G (5.6%). 14 patients harbored IDH2 active-site mutations, including IDH2-R172W (78.6%), IDH2-R172K (7.14%), IDH2-R172M (7.14%) and IDH2-R140Q (7.14%). Among the 50 activating IDH mutations patients, co-variations in TP53 (7, 14%), KRAS (7, 14%), ARID1A (7, 14%), KMT2C (3, 6%) and BAP1 (3, 6%) were observed. Compared to other patients, the activating IDH mutations group had a relatively lower TMB (Median 3.97 vs 2.86, p=0.09).

Conclusions: We elucidate the molecular and clinicopathological characteristics of IDH mutant BDCs from a large number of Chinese patients to provide foundational knowledge on personalized clinical management for IDH-directed therapy.

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58P Intrahepatic cholangiocarcinoma (iCCA) hidden amongst the unknown: A retrospective analysis of cancer of unknown primary (CUP) cases from a tertiary cancer centre

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Background: Many patients (pts) with CUP present with presumed metastatic disease to the liver. Due to lack of definitive histological markers, iCCA may be an overlooked diagnosis. With the emergence of efficacious molecularly targeted therapies in iCCA, this study assessed the potential frequency of iCCA (previously not identified) within a CUP cohort.

Methods: A single-centre retrospective study of sequential pts referred to a regional CUP multi-disciplinary team (MDT) (Jan 2017 - Apr 2020) was performed. Demographic data, histopathology, MDT history, treatment/survival outcomes were collected. For pts presenting with liver involvement, baseline diagnostic imaging was reviewed independently by a hepatobiliary radiologist and/or oncologist. Pts with radiological features of iCCA (dominant liver lesion, capsular retraction) were identified. For a subset of pts molecular characterisation of tumour tissue was performed.

Results: Of 233 pts referred to the CUP MDT, 74 pts had malignancy involving the liver. For 13 of these pts, a primary tumour diagnosis (different primaries) was subsequently established. Of the remaining liver-involved CUP cohort (n=61), 56 pts had evaluable radiology reviewed and 25 (43%) had radiological features consistent with iCCA. These 25 pts were predominantly female (n=19; 77%) with a median age of 65 years (range 31-79). 64% had an ECOG PS $\leq$2 and 50% received first line platinum-based chemotherapy. Molecular alterations (IDH mutations/FGFR fusions) supporting an iCCA diagnosis were detected in a subset of pts where testing was performed. Median overall survival (OS) of the potential iCCA group (n=25) and remaining liver-involved CUP group (not iCCA) were similar (OS 3.8 vs 3.9 months, logrank p-value = 0.805); comparatively, patients with subsequent primary diagnosis (and liver-involvement, n=13) had significantly better OS (10.2 months, logrank p-value = 0.0227).

Conclusions: In this study 41% of patients referred with liver-involved CUP, matched the radiological criteria for an iCCA diagnosis, highlighting the importance of identifying these pts within CUP cohorts, ensuring correct diagnosis, molecular characterisation and treatment.

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59TiP Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121)

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Background: Biliary tract cancer (BTC) is an aggressive disease with a poor prognosis. Gemcitabine + cisplatin (GemCis) is the accepted global standard of care; however, key cancer resistance mechanisms associated with the transport, activation and breakdown of gemcitabine are known to limit its clinical activity. NUC-1031 is a phosphoramidate transformation of gemcitabine designed to overcome these key resistance mechanisms and generate much higher levels of the active anti-cancer metabolite, dFdCTP, in cells. Promising efficacy has been observed in the phase Ib ABC-08 study of NUC-1031 + cisplatin for first-line treatment of advanced BTC. Of 21 patients (pts) enrolled in 2 dose cohorts (NUC-1031 625 mg/m^2 or 725 mg/m^2 + cisplatin 25 mg/m^2 on Days 1 and 8 of 21-day cycles), 16 were considered to be efficacy evaluable. In this population, 1 pt had a CR and 6 pts had PRs, resulting in an ORR of 44% (7/16). This compares favorably to the 26% ORR reported for GemCis. In addition, 6 pts had SD, resulting in a DCR of 81% (13/16). The combination was well tolerated with no unexpected AEs or DLTs. The recommended dose of NUC-1031 with cisplatin was 725 mg/m^2. The encouraging efficacy and tolerability profile led to initiation of a global registrational study.

Trial design: NuTide:121 is a phase III, open-label, randomised study of NUC-1031 + cisplatin vs GemCis for first-line treatment of advanced BTC. Pts $\geq$18 years with histologically- or cytologically-confirmed BTC (including cholangiocarcinoma, gallbladder, or ampullary cancer), who have had no prior systemic chemotherapy for locally advanced/metastatic disease, are eligible. A total of 828 pts are being randomised (1:1) to either 725 mg/m^2 NUC-1031 or 1000 mg/m^2 gemcitabine, both with 25 mg/m^2 cisplatin, administered on Days 1 and 8 of 21-day cycles. Primary endpoints are OS and ORR. Secondary endpoints include PFS, safety, PK and pt-reported QoL. In addition to the final analysis, three interim analyses are planned. NuTide:121 is being conducted at approximately 125 sites across North America, Europe and Asia Pacific.

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