Conclusions: EBV-associated intrahepatic cholangiocarcinoma is rare with the prevalence of EBV- 7.5%. EBV positive patients tend to present at a very early stage and carry a good prognosis.

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76P The distribution of tumor mutational burden in IDH-mutant solid tumors

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Background: Isocitrate dehydrogenase (IDH) is an enzyme family involved in cell aerobic metabolism of tricarboxylic acid cycle. In addition to gliomas and acute myeloid leukemia, *IDH* mutations have been found in approximately 75% of chondrosarcomas, 10-23% of biliary tract cancer (BTC), and a small number of other tumors. IDH inhibitors have shown promising efficacy in cholangiocarcinoma patients harboring *IDH1* mutations. However, the distribution of tumor mutational burden in IDH-mutant solid tumors has not been fully characterized.

Methods: Tissue were subjected to NGS in a College of American Pathologists-certified and Clinical Laboratory Improvement Amendments-accredited lab for detection the IDH mutation.

Results: A total of 317 *IDH* mutated patients from 5 solid tumor species were analyzed, including biliary carcinoma (81 cases), liver cancer (66 cases), lung cancer (85 cases), colorectal cancer (61 cases) and gastric cancer (24 cases). The average age for patients harboring IDH mutations was 60 years (range, 25-86 years). Among all the IDH mutations cases, the most common *IDH* variant were *IDH1* and *IDH2* which were discovered in 183 cases (57.7%) and 106 cases (33.4%), respectively. The TMB were significantly higher in lung cancer, colorectal cancer and gastric cancer than BTC ($p=$ 0.0164, $p<0.0001$, $p=$ 0.0067, respectively). In addition, we also analyzed the relationship between *IDH* mutation/wild-type with TMB in BTC (n=907). Patients with *IDH* mutation (n=72) had lower TMB compared with patients with wild-type *IDH* ($p=$ 0.0236).

Conclusions: Our findings suggest that *IDH* mutation may be a potential driving mutation gene of BTC which can independently lead to the development of tumor. But in other tumors it may be only co-mutation gene.

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77P Clinical characteristics and therapeutic implications of PALB2 variants in patients with advanced solid tumors

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Background: Partner and Localizer of BRCA2 (PALB2) is a nuclear protein that localizes to sites of DNA double-strand breaks and interacts with BRCA1 and BRCA2 to promote DNA repair. *PALB2* germline mutations are associated with an increased risk of hereditary cancers. *PALB2* somatic variants have been found in various cancers; however, their prevalence, functional impact and therapeutic implications in cancers remains largely unknown.

Methods: Next-generation sequencing (NGS) data from patients (pts) with advanced cancers treated at MD Anderson Cancer Center were reviewed to identify tumors with *PALB2* variants and co-occurring genomic alterations. Demographics, histopathology, and treatment response data were collected through retrospective chart review. The intervar *in-silico* tool was used to classify *PALB2* variant pathogenicity.

Results: NGS data from 13,599 pts identified *PALB2* variants in 219 (~1.6%) pts, comparable to 2.1% of *PALB2* alterations in the TCGA PanCancer database. Of these 219 pts, *PALB2* variants were annotated as follows: 44 (20%) as pathogenic or likely pathogenic, 88 (40%) as benign or likely benign, 78 (36%) as variants of unknown significance (VUS) and 9 (4%) as indeterminate. 501 unique co-occurring mutations were identified, including *TP53* (83%), *LRP1B* (38%), *PIK3CA* (34%), *NF1* (32%) and *MLL2* (30%). The most common cancers with *PALB2* alterations were cholangiocarcinoma (15%), breast (11%), melanoma (10%), colon (10%) and non-small cell lung cancer (8%). Of 31 pts with advanced cholangiocarcinoma and *PALB2* alterations, 2 had germline *PALB2* mutations. 22/31 (71%) received platinum-based therapy and had evaluable response data; 9/22 (41%) pts achieved radiological partial response (PR), 1/22 (5%) had stable disease (SD), 12/22 (55%) had progressive disease, for a clinical benefit rate (PR+SD) of 45.5% with mean therapy duration of 137 days (range 42- 476).

Conclusions: *PALB2* variants were detected in different cancers, including cholangiocarcinoma. Patients with advanced cholangiocarcinoma and *PALB2* alterations may derive greater benefit from platinum-based therapy versus historical controls. *PALB2* alterations warrant further investigation as predictive biomarkers of response to platinum-based therapy.

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78TiP KEYNOTE-966 trial in progress: Pembrolizumab plus gemcitabine and cisplatin for advanced biliary tract cancer

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Background: Biliary tract cancer (BTC), comprising intra- and extra-hepatic cholangiocarcinoma and gallbladder cancer, is a rare and aggressive malignancy. Most patients (pts) present with advanced or unresectable disease, for which the current standard of care is gemcitabine plus cisplatin. Median survival for these pts is only 12 months, highlighting the need for more effective therapies. Pembrolizumab is a PD-1

inhibitor that has demonstrated modest antitumor activity as monotherapy in pts with previously treated BTC and has improved survival when used in combination with platinum-based chemotherapy in other cancer types.

Trial design: KEYNOTE-966 (NCT04003636) is a randomized, double-blind, phase III trial designed to evaluate the efficacy and safety of pembrolizumab plus gemcitabine and cisplatin versus placebo plus gemcitabine and cisplatin in pts with previously untreated advanced BTC. Key eligibility criteria include age $\geq$18 years, histologically confirmed metastatic or unresectable BTC, measurable disease per RECIST v1.1, ECOG performance status 0/1, and no prior systemic therapy for advanced BTC. Pts with past or ongoing hepatitis C or controlled hepatitis B virus infection are eligible per protocol-defined criteria. Approximately 788 pts will be randomly allocated 1:1 to pembrolizumab 200 mg or placebo IV every 3 weeks in combination with gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 IV on days 1 and 8 of every 3-week cycle. Pembrolizumab will be continued for $\leq$35 cycles or until progression, unacceptable toxicity, or withdrawal. Gemcitabine will be continued until progression, unacceptable toxicity, or withdrawal. Cisplatin will be given for a maximum of 8 cycles. Primary endpoints are progression-free survival and overall survival. Secondary endpoints are objective response rate, duration of response, and safety. Exploratory endpoints include disease control rate and health-related quality of life. Tumor imaging by CT or MRI will be performed every 6 weeks until week 54, and every 12 weeks thereafter. Adverse events will be monitored throughout the study and graded according to NCI CTCAE v.5.0. Recruitment began in September 2019 and is underway in 19 countries.

Clinical trial identification: NCT04003636.

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79TiP A phase II/III, randomized, placebo-controlled study of bintrafusp alfa with gemcitabine plus cisplatin as first-line treatment of biliary tract cancer

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Background: Gemcitabine + cisplatin is the current standard of care for first-line treatment of patients with locally advanced/metastatic biliary tract cancer (BTC), but survival outcomes are poor. Aberrant TGF-β signaling may be associated with BTC pathogenesis; TGF-β activity in tumors may lead to resistance to anti–PD-(L)1 therapies. Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. In murine models, the combination of bintrafusp alfa and chemotherapy resulted in improved antitumor activity over either therapy alone. Bintrafusp alfa monotherapy previously demonstrated clinical activity and manageable safety in BTC for which standard chemotherapy failed in an expansion cohort from a phase I study (NCT02699515); the objective response rate (ORR) was 20% per independent review. In this phase II/III study, the efficacy and safety of bintrafusp alfa and gemcitabine + cisplatin vs gemcitabine + cisplatin will be evaluated.

Trial design: This multicenter, phase II/III study (NCT04066491) of patients with histologically/cytologically confirmed BTC, including intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer, has an open-label safety run-in part and a randomized, double-blind, placebo-controlled part. Patients may not have received treatment for locally advanced/metastatic disease and must have an ECOG performance status of $\leq$1. Patients who have had interstitial lung disease will be excluded. In the open-label safety run-in part, $\geq$12patients will receive bintrafusp alfa (2400 mg Q3W) and gemcitabine + cisplatin (D1 and D8 Q3W for 8 cycles) followed by bintrafusp alfa monotherapy (2400 mg Q3W). In the randomized part, $\leq$500 patients will be randomized 1:1 to receive bintrafusp alfa (2400 mg) or placebo Q3W in addition to gemcitabine + cisplatin (D1 and D8 Q3W for 8 cycles). The primary endpoint of the randomized part is overall survival; key secondary endpoints include progression-free survival, ORR, and safety. Estimated enrollment is 512 patients.

Clinical trial identification: NCT04066491.

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