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1012P Analysis of tumor location related oncologic characteristics of hepatocellular carcinoma

W. Fan[1], H. Zhang[2], D. Tian[3], T. Li[3], Y. Bai[3], M. He[3], Y. Liu[1], Y. Gong[1], X. Xu[1]

[1]Department of Hepatobiliary Surgery, Guizhou Provincial People's Hospital, Guiyang, China; [2]The Medical Department, 3D Medicines Inc., Shanghai, China; [3]Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Kunming Medical University, Kunming, China

Background: Immune checkpoint inhibitors (ICI) therapy is not suitable for all patients with cancer, and hepatocellular carcinoma (HCC) included, it depend largely on characteristics of tumor and biomarkers, We analyzed features of HCC related to biomarkers of immunotherapy such as tumor mutation burden (TMB), PD-L1 expression, and gene landscape, and mainly focused on the tumor location.

Methods: Tumor samples of 173 HCC patients were consecutively collected in China from January 2018 to November 2019, gene mutation and TMB level were analyzed by next generation sequencing (NGS), detected PD-L1 expression by using Dako PD-L1 IHC 22C3 pharmDx, Tumor Proportion Score (TPS) was used to determine expression of PD-L1. TPS was arranged into the following intervals: strong positive $\geq$50%, moderate positive $\geq$5% and $<$50%, weak positive $\geq$1% and $<$5%, and negative $<$1%.

Results: All these tissue samples were divided as right (n=118) and left (55) hepatic lobe according anatomical location, NGS analysis showed that, higher mutation frequency of several genes, such as CTNNB1 (22.0% Vs 10.9%), CCND1 (6.8% Vs 1.8%), KEAP1 (10.2% Vs 1.8%), SMAD4 (5.1% Vs 1.8%) were found in right than in left hepatic lobe ($p<0.05$); while several other gene such as ARID1A (23.6% Vs 13.6%), ARID2 (14.5% Vs 5.1%), ALB (12.7% Vs 1.7%), were mutated more frequently in left than right hepatic lobe ($p<0.05$). TMB level was significantly different in right and left hepatic lobe ($p<0.05$), the media TMB level was 7.13 and 4.3 mutations/Mb for right and left hepatic lobe, respectively. Among these 173 HCC patients, 104 were detectable for PD-L1 expression. 32% (24/74) of right hepatic lobe were PD-L1 positive, 27% (8/30) of left were PD-L1 positive. Percentage of individuals had TPS as strong positive (2.7% Vs 0) and moderate positive (1.3% Vs 6.7%) were different between right and left hepatic lobe, while no significant difference was found for percentage of individuals had TPS as weak positive and negative.

Conclusions: Different anatomical sites of liver cancer hold different gene landscape, level of TMB and PD-L1 expression, this suggest HCC patients with different tumor location should be treated differently in the clinic, especially, for using immune checkpoint inhibitors.

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1013P PTPN13 inactivation by hepatitis B virus X regulates metabolic reprogramming for hepatocellular carcinoma progression

Y. Yan, K. Mao, C. He, H. Liu, J. Zhang, J. Wang, Z. Xiao

Hepatobiliary Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: Hepatitis B x protein (HBx) participates in the tumorigenesis and progression of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). PTPN13 is a significant regulator in tumor development, however, its specific role in hepatocarcinogenesis remains to be explored. We herein explore the function and mechanism of PTPN13-triggered metabolic reprogramming in HBV related hepatocarcinogenesis.

Methods: QRT-PCR, Western blotting, and immunohistochemistry were used to analyze HCC cell lines, and human and mouse HCC tumor tissues, and to correlate PTPN13 expression with patient prognosis. The underlying regulatory mechanisms were studied with both ex vivo analyses and vitro experiments, such as immunoprecipitation, Chromatin immunoprecipitation and Electrophoretic mobility shift assay, mammalian two-hybrid system and RNA-binding protein immunoprecipitation.

Results: Decreased PTPN13 expression was associated with HBV/HBx. Patients with low PTPN13 expression showed a poor prognosis. Functional assays revealed that PTPN13 inhibited proliferation and tumorigenesis. Further mechanistic studies indicated that HBx inhibited PTPN13 expression by upregulating the expression of DNMT3A and interacting with DNMT3A. Furthermore, we found that DNMT3A bound to the PTPN13 promoter (-343$\sim$-313 bp) in an epigenetically controlled manner associated with elevated DNA methylation and then inhibited PTPN13 transcription. Additionally, we identified IGF2BP1 as a novel PTPN13-interacting gene and demonstrated that PTPN13 influences c-Myc expression by directly and competitively binding to IGF2BP1 to decrease the intracellular concentration of IGF2BP1. Importantly, we discovered that the PTPN13-IGF2BP1-c-Myc axis was important for cancer cell growth through promoting metabolic reprogramming. We verified the significant negative correlations between PTPN13 expression and c-Myc, PSPH, and SLC7A1 expression in HCC tissues.

Conclusions: PTPN13 is a novel regulator of HBV-related hepatocarcinogenesis and may play an important role in HCC. PTPN13 may serve as a prognostic marker and therapeutic target in HBV-related HCC patients.

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1014TiP PROOF: A multicenter, open-label, randomized, phase III trial of infigratinib vs gemcitabine + cisplatin in patients with advanced cholangiocarcinoma with FGFR2 gene rearrangements

G.K. Abou-Alfa[1], I. Borbath[2], A.L. Cohn[3], L. Goyal[4], A. Lamarca[5], T. Macarulla[6], D-Y. Oh[7], S. Roychowdhury[8], S. Sadeghi[9], R.T. Shroff[10], M. Howland[11], A. Li[12], T. Cho[13], A. Pande[14], M. Javle[15]

[1]Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Medical Oncology, Cliniques universitaires St Luc Bruxelles, Brussels, Belgium; [3]Medical Oncology, Rocky Mountain Cancer Center, Denver, CO, USA; [4]Medical Oncology, Massachusetts General Hospital, Boston, MA, USA; [5]Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [6]Medical Oncology, Hospital Vall d'Hebron, Barcelona, Spain; [7]Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea; [8]Medical Oncology, Ohio State Comprehensive Cancer Center/James Cancer Hospital, Columbus, OH, USA; [9]Medical Oncology, University of California at Los Angeles, Santa Monica, CA, USA; [10]Medical Oncology, University of Arizona Cancer Center, Tucson, AZ, USA; [11]Clinical Science, QED Therapeutics Inc., San Francisco, CA, USA; [12]Biometrics, QED Therapeutics Inc., San Francisco, CA, USA; [13]Clinical Operations, QED Therapeutics Inc., San Francisco, CA, USA; [14]Clinical Development, QED Therapeutics Inc., San Francisco, CA, USA; [15]Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

Background: Cholangiocarcinoma (CCA) treatment options are limited with a need to provide better disease control, improved outcome, and targeted therapy that is less toxic than standard chemotherapy. As the understanding of the molecular landscape of CCA has increased, the fibroblast growth factor receptor (FGFR) family has been found to play an important role in CCA. *FGFR* gene fusions and rearrangements represent driver mutations; they are present in 13−17% of intrahepatic CCA and may predict tumor sensitivity to FGFR inhibitors. Infigratinib (BGJ398) is an ATP-competitive, FGFR1−3 selective oral tyrosine kinase inhibitor. Based on promising preliminary response data of infigratinib in patients with relapsed/refractory CCA with *FGFR2* gene fusions or other rearrangements (phase II trial CBJG398X2204), the PROOF trial is evaluating infigratinib vs gemcitabine + cisplatin in front-line patients with advanced CCA with *FGFR2* gene rearrangements.

Trial design: Patients with advanced/metastatic or inoperable CCA with *FGFR2* gene fusions (determined by local or central laboratory) are randomized 2:1 to oral infigratinib once daily for 21 days of a 28-day treatment cycle vs intravenous standard gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) on days 1 and 8 of a 21-day cycle. Treatment will continue until confirmed progressive disease by central review, intolerance, withdrawal of informed consent, or death. Patients on the gemcitabine + cisplatin arm who develop disease progression can cross-over to receive infigratinib. The primary endpoint is progression-free survival (PFS, RECIST v1.1 central review). Secondary endpoints include overall survival, PFS (investigator determined), overall response rate, disease control rate, duration of response, and safety. Quality of life, pharmacokinetics and exploratory genetic alterations/biomarkers will also be measured. The trial will have sites in the US, EU, and APAC, including Australia. Enrollment is ongoing.

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1015TiP Ramucirumab in patients with advanced hepatocellular carcinoma and elevated alpha fetoprotein following a non-sorafenib based systemic therapy: An expansion cohort of the phase III REACH-2 study

R.S. Finn[1], S-K. Qin[2], P.R. Galle[3], C. Wang[4], K.D. Ogburn[4], R. Widau[4], A.X. Zhu[5]

[1]Department of Medicine, Division of Hematology and Oncology, University of California, Los Angeles Medical Center, Los Angeles, CA, USA; [2]Department of Medical Oncology, Cancer Center of People's Liberation Army, 81 Hospital of People's Liberation Army, Nanjing, China; [3]First Department of Internal Medicine, University Medical Center Mainz, Mainz, Germany; [4]Oncology, Eli Lilly and Company, Indianapolis, IN, USA; [5]Medical Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

Background: Ramucirumab (an IgG1 vascular endothelial growth factor receptor-2 antagonist) is the first and only treatment approved in a biomarker-selected population with advanced hepatocellular carcinoma (HCC). Ramucirumab was approved in HCC based on data from patients with alpha-fetoprotein (AFP) levels ≥400 ng/mL in the phase III REACH (NCT01140347) and REACH-2 (NCT02435433) studies. Similar to other contemporary studies, the REACH-2 intention-to-treat (ITT) population did not include patients who received first-line systemic therapy other than sorafenib, since sorafenib was the only treatment with demonstrated overall survival (OS) benefit when the studies were initiated. This global, open-label expansion (OLE) cohort of REACH-2 was initiated to study ramucirumab in patients with advanced HCC and baseline AFP ≥400 ng/mL following non-sorafenib based systemic therapy.

Trial design: This single-arm, open-label, global OLE investigates ramucirumab in patients with advanced HCC who received 1-2 lines of prior systemic therapy for HCC other than sorafenib or chemotherapy (i.e. a tyrosine kinase inhibitor as monotherapy or in combination with an immune checkpoint inhibitor). Eligible patients will have Barcelona Clinic Liver Cancer stage C or B disease (refractory or not amenable to locoregional therapy), Child-Pugh class A liver disease, an Eastern Cooperative Oncology Group performance status of 0/1, and baseline AFP ≥400 ng/mL. Patients who received a prior liver transplant are eligible. Approximately 44 patients will be enrolled to receive ramucirumab 8 mg/kg intravenously once every 14 days. The primary objective is safety. Secondary objectives are OS, progression-free survival, time to radiographic progression, objective response rate, pharmacokinetics, immunogenicity, and patient-reported outcomes. All analyses of the OLE will be independent of the main randomized, double blind, placebo-controlled ITT cohort of REACH-2.

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1016TiP LEAP-012 trial in progress: Pembrolizumab plus lenvatinib and transarterial chemoembolization (TACE) in patients with intermediate-stage hepatocellular carcinoma (HCC) not amenable to curative treatment

J.M. Llovet[1], A.B. El-Khoueiry[2], A. Vogel[3], D.C. Madoff[4], R.S. Finn[5], S. Ogasawara[6], Z. Ren[7], K. Mody[8], J. Jing Li[9], A.B. Siegel[9], L. Dubrovsky[9], M. Kudo[10]

[1]Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Clinical Investigations Support Office, USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [3]Department of Gastroenterology, Hepatology, and Endocrinology, Hannover Medical School, Hannover, Germany; [4]Department of Radiology and Biomedical Imaging, Yale School of Medicine, Yale Cancer Center and Yale New Haven Health, Smilow Cancer Hospital, New Haven, CT, USA; [5]Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [6]Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan; [7]Medical Oncology, Zhongshan Hospital Fudan University, Shanghai, China; [8]Oncology Clinical Research, Eisai Inc., Woodcliff Lake, NJ, USA; [9]Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA; [10]Department of Gastroenterology and Hepatology, School of Medicine, Kindai University, Osaka, Japan

Background: Standard of care for intermediate HCC ineligible for curative treatment is locoregional therapy with transarterial chemoembolization (TACE). Lenvatinib, an inhibitor of VEGFRs 1-3, FGFRs 1-4, PDGFR α, RET, and KIT, is a first-line option for advanced HCC. Pembrolizumab is a PD-1 inhibitor; data from a phase Ib trial of lenvatinib plus pembrolizumab showed broad antitumor activity and manageable safety in patients with unresectable intermediate HCC not amenable to TACE. LEAP-012 (NCT04246177) is a randomized, double-blind, phase III trial to investigate lenvatinib plus pembrolizumab vs placebo in combination with TACE in patients with intermediate HCC.

Trial design: Eligible patients are ≥18 y with confirmed HCC localized to the liver without portal vein thrombosis and not amenable to curative treatment. Patients must have ≥1 measurable lesion per RECIST v1.1 and ECOG PS of 0/1. Patients previously treated with locoregional therapy (≤4 weeks) or systemic chemotherapy for HCC are excluded. Approximately 950 patients will be randomly assigned 1:1 to receive oral lenvatinib QD (12 mg ≥60 kg; 8 mg <60 kg) plus IV pembrolizumab 400 mg Q6W plus TACE or oral placebo QD plus IV placebo Q6W plus TACE. Lenvatinib will be administered until progression or unacceptable toxicity; pembrolizumab will be administered for up to 2 years. TACE is limited to 2 treatments per lesion per site-specified modality. Patients will be stratified by study site, α-fetoprotein level, ECOG PS, albumin−bilirubin grade, and tumor burden. Imaging will be performed every 9 weeks. Safety will be assessed throughout the study. Coprimary end points are overall survival and progression-free survival. Secondary end points are objective response rate, disease control rate, duration of response, time to progression, and safety. Exploratory end points include time from randomization to second/subsequent progression, molecular biomarkers, and health-related quality of life. Recruitment for this study began in April 2020.

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