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

K. Shitara[1], T. Golan[2], K. Mileham[3], M. Voskoboynik[4], S. Rha[5], M. Gutierrez[6], R. Perets[7], S. Taylor[8], D. Chen[9], T. Keenan[9], M. Rajasagi[9], J. Healy[9], H. Shoji[10]

[1]National Cancer Center Hospital, Tokyo, Japan; [2]The Oncology Institute, Sheba Medical Center at Tel HaShomer, Tel Aviv University, Tel Aviv, Israel; [3]Levine Cancer Institute, Atrium Health, Charlotte, United States; [4]Alfred Health and Central Clinical School, Monash University, Melbourne, Australia; [5]Yonsei Cancer Center, Yonsei University College of Medicine, Seodaemun-gu, Seoul, South Korea; [6]Hackensack University Medical Center, Hackensack, United States; [7]Division of Oncology, Clinical Research Institute at Rambam, Rambam Medical Center and Technion-Israel Institute of Technology, Haifa, Israel; [8]University of Pittsburgh Medical Center, Pittsburgh, United States; [9]Merck & Co., Inc., Kenilworth, United States; [10]Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

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.

Clinical trial identification: NCT02964013.

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

S. Park[1], G. Song[2], H. Seo[2], S. Lee[3], D. Kim[2], A. Jang[4]

[1]Kosin University Gopspel Hospital, Busan, South Korea; [2]Pusan National University Hospital, Busan, South Korea; [3]Ulsan National Institute of Science and Technology, Ulsan, South Korea; [4]Department of Nursing Ulsan University, Ulsan, South Korea

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

M. Rimini[1], C. Fabregat[2], V. Burgio[1], S. Lonardi[3], M. Niger[4], M. Scartozzi[5], I. Rapposelli[6], G. Aprile[7], F. Ratti[1], F. Pedica[1], T. Macarulla[8], M. Fassan[9], A. Pretta[10], F. Simionato[11], F. De Cobelli[1], L. Aldrighetti[1], L. Fornaro[12], S. Cascinu[13], A. Casadei Gardini[1]

[1]San Raffaele Hospital, Milan, Italy; [2]Hospital Vall D'Hebron, Barcelona, Spain; [3]Medical Oncology, Veneto Institute of Oncology IRCCS, Padua, Italy; [4]Fondazione Istituto Nazionale Tumori IRCCS, Milan, Italy; [5]Medical Oncology Unit, University Hospital and University of Cagliari, Monserrato, Italy; [6]Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS, Meldola, Italy; [7]Department of Oncology, San Bortolo General Hospital, Azienda ULSS8 Berica, Vicenza, Italy; [8]Hospital Vall D'Hebron, Barcelona, Spain; [9]Medical Oncology Unit, Department of Oncology, Veneto Institute of Oncology IRCCS, Padua, Italy; [10]Medical Oncology Unit, Sapienza University of Rome - University Hospital and University of Cagliari, Monserrato, Italy; [11]Department of Oncology, San Bortolo General Hospital, ULSS8 Berica - East District, Vicenza, Italy; [12]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [13]IRCCS Ospedale, San Raffaele Scientific Institute, Milan, Italy

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