

models. Moreover, in dMMR cases, a custom in-house Next-Generation Sequencing (NGS) (Ion Torrent S5) panel was performed, assessing mutational status of 26 tumor genes (EGFR, MET, ALK, RET, KRAS, NRAS, HRAS, BRAF, KIT, PDGFR  $\alpha/\beta$ , GNAQ, GNA11, PIK3CA, AKT1, MAP2K1, MAP2K2, TP53, ERBB2, SMAD4, PTEN, STK11, CTNNA1, NOTCH1, POLE, ESR1).

**Results:** We selected 76 out of 90 patients, with a median age at diagnosis of 61 years. Fifty-nine patients received NAC, while 17 were treated with adjuvant chemotherapy alone. Overall, dMMR/MSI-H counted for 8% of cases, entirely consistent between endoscopic and surgical samples. Six percent of tumors were HER2 positive on endoscopic tumor assessment and 4% on surgical samples. Tumor downstaging was observed in 52.5% of the population, with 3 pCR (5.1%), none of them in MSI-H cancers. According to MSI status and pCR, EFS and OS were better for MSI-H patients and MSS achieving pCR compared to MSS without pCR [EFS NR vs NR vs 30.0 months (95% CI 16.8 – NR.),  $P = .08$ ; OS NR vs NR vs 39.6 (95% CI 27.6 – NR)  $P = .10$ ]. Considering the entire population, EFS and OS were analyzed according to MSI status with a better outcome for MSI-H patients [EFS NR vs 48.0 months (95% CI 25.2 – 229.4),  $P = .121$ ; OS NR vs 62.4 (95% CI 28.8 – 229.4)  $P < .143$ ]. The most common alteration in MSI-H cases was TP53 mutation (4/6), other mutations detected were KRAS, SMAD4, ERBB2, BRAF, PIK3CA, RET and PTEN.

**Conclusions:** Our work confirms the positive prognostic effect of MSI-H in the curative setting of LAGC, not correlated with the rate of pathologic tumor response to NAC. Prospective ad-hoc trial focused on dMMR/MSI-H and more accurate molecular profiling are strongly needed in resectable LAGC.

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#### P-47 Inhibition of phosphoprotein phosphatase 2A (PP2A) sensitizes pancreatic cancer to PARP inhibitors by modulation of homologous recombination repair

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**Background:** Pancreatic cancer remains one of the most difficult to treat cancers with a 5-years survival of less than 6%, representing one of the most lethal types of cancer, recent research has shown that PP2A inhibitors (LB-100) sensitize pancreatic cancer to chemotherapy and radiation. In addition, the finding from clinical trial study demonstrated that the effectiveness of single-agent Talazoparib for treatment of patients with and without germline BRCA1/2 mutation in ovarian, breast, small cell lung and Pancreatic cancers. The aim of this work was to I. investigate activity of LB-100 against pancreatic cancer cells as monotherapy and in combination with PARP inhibitors (Talazoparib). II. Investigate the mechanism by which LB-100 and Talazoparib effect pancreatic cancer cells by studying effect of drugs on cell cycle and modulation of cell cycle regulatory proteins and assess the role of treatment combination in control DSB and HR repair through modulation of ATM phosphorylation.

**Methods:** Human pancreatic cancer cell lines Panc-1, MIA-Pa-Ca-2 and BxPC-3 were obtained from European Collection of Authenticated Cell Culture (ECACC) and grown in either Dulbecco's modified Eagle medium (DMEM) (MiaPaCa-2 and Panc-1) or RPMI medium (BxPC-3) with 10% FBS. Cell cultures were maintained in an atmosphere of 5% CO<sub>2</sub>/95% air at 37 °C. PP2A activity was measured by PP2A Immunoprecipitation phosphatase assay Kit (Millipore), cell cytotoxicity were measured by MTT assay, cell cycle determined by flow cytometry. Western blot techniques were used to assess levels of proteins associated with regulation of cell cycle (Cdc2, p-Cdc2, and Cdc25c), apoptosis (caspase3) and DNA damage ( $\gamma$ -H2AX). Data are expressed as the mean  $\pm$  (SEM) and analysed by an analysis of variance (ANOVA).

**Results:** The results show that LB-100 decreased PP2A activity in all pancreatic cancer cells in dose dependent manner. LB-100 significantly decreased cell viability of Panc-1, MIA-Pa-Ca-2 and BxPC-3 with IC<sub>50</sub> (3.94  $\mu$ M, 6.86  $\mu$ M, and 10.87  $\mu$ M) respectively. Interestingly adding 25 nm of Talazoparib further decreased IC<sub>50</sub> in all cells (1.88  $\mu$ M, 5.24  $\mu$ M and 5.83  $\mu$ M). Treatment combination attenuated pancreatic cancer cells growth through caspase activation and G2/M cell-cycle arrest. Combination therapy impaired cellular repair and induced DNA double-strand breaks by inducing  $\gamma$ -H2AX.

**Conclusions:** Our results suggest that treatment combination of LB100 and talazoparib in vitro inhibit cancer cells growth by modulation of the DNA damage response pathway and cell cycle checkpoint abrogation. The combination of PP2A inhibitor with PARP inhibitor has a synergistic effect in vitro. Further in vivo studies are needed to explore this combination as an effective option in the treatment of pancreatic cancer.

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#### P-48 Phase 2a study of NT-17, a long-acting interleukin-7, plus pembrolizumab: Cohort of subjects with checkpoint inhibitor-naïve advanced pancreatic cancer

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**Background:** Pancreatic cancer (PaC) is immune-quiescent and resistant to single-agent checkpoint inhibitor (CPI). NT-17 (efineptakin alfa) is a long-acting IL-7 that can increase T-cell infiltration in the tumor microenvironment (TME) and may enhance tumor responsiveness to CPI therapy. We hypothesize that the combination of NT-17 and pembrolizumab may result in enhanced efficacy in CPI-naïve advanced PaC.

**Methods:** This is an open-label, phase 2a study in subjects with relapsed/refractory (R/R) tumors, including CPI-naïve R/R PaC. The study follows Simon's 2-stage minimax design to enroll 17 in the first stage, and 8 additional subjects in the second stage. Subjects received NT-17 intramuscularly at 1200  $\mu$ g/kg every 6 weeks (Q6W) plus pembrolizumab 200 mg intravenously Q3W. Antitumor activity based on Overall Response Rate (ORR) was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and iRECIST. Biomarker analyses of peripheral blood and tumor biopsies were performed.

**Results:** As of 14-March-2022, 32 subjects were enrolled in the CPI naïve R/R PaC cohort. Median age was 66 years [31-81], with ECOG PS 0 (31%), 1 (69%). Twenty-eight (90.3%) subjects had  $\geq 2$  prior therapies. All subjects had metastatic or locally advanced disease at enrollment. The median duration of follow-up was 3.7 months. Among 26 evaluable subjects, the ORR and disease control rate (DCR) were 4% (1/26) and 31% (8/26) by RECIST 1.1; 8% (2/26) and 35% (9/26) per iRECIST. In addition to 2 subjects with iPR, 9 subjects are still ongoing to follow up responders. It was observed that among subjects with  $\leq 1$  liver mets vs  $\geq 2$  liver mets, the ORR by iRECIST was 18.2% (2/11) vs 0; DCR was 63.7% (7/11) vs 13.3% (2/15) and PFS was 19.1 weeks vs 6.0 weeks. The ORR and DCR by iRECIST were 25% (1/4) and 75% (3/4) in 1L; 13% (1/8) and 38% (3/8) in 2L. All subjects with responses continue treatment. NT-17 treatment-related adverse events (trAEs) occurred in 23 (71.9%) subjects, 18 (56.2%) G1-2, 3 (9.4%) G3; 2 (6.3%) G4; no G5 trAEs were reported. No subjects discontinued from treatment due to trAE. A cPR subject with available biopsy had enhanced T-cell infiltration in the TME at week 5.

**Conclusions:** The chemotherapy-free combination of NT-17 + pembro was well tolerated in heavily pretreated subjects with CPI-naïve R/R PaC. The encouraging antitumor activity showed that subjects with  $\leq 1$  liver mets achieved clinical benefit from the combination of NT-17 and pembro therapy. Biomarker analyses demonstrated improved peripheral and intratumoral T cell responses. These results support continued evaluation of NT-17 + pembrolizumab in subjects with CPI-naïve R/R PaC.

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