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P-49 GOBLET: A phase 1/2 multiple indication signal finding and biomarker study in advanced gastrointestinal cancers treated with pelareorep and atezolizumab — safety and preliminary response results

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Background: In GI cancers, checkpoint inhibitors are only effective in patients with high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) tumors. Oncolytic viruses may improve the susceptibility of microsatellite stable (MSS) tumors to immunotherapy by modifying the tumor microenvironment (TME). Pelareorep (pela) is an intravenously delivered, non-genetically modified, oncolytic reovirus that mediates cancer cell killing by activating innate and adaptive immune responses directed against the tumor as well as direct tumor oncolysis. Accordingly, treatment with pelareorep results in increased T cell infiltration and PD-L1 expression in tumors which primes the TME for responsiveness to checkpoint inhibitors. Pela has demonstrated activity in many cancers including colorectal and pancreatic cancer. The GOBLET study is designed to assess the efficacy of pela plus atezolizumab (atezo) with or without chemotherapy in multiple GI cancers.

Methods: GOBLET is a phase 1/2, open-label, non-randomized study in patients with advanced or metastatic GI cancers and utilizes a Simon two-stage design. In the first stage of the study, four treatment groups are being enrolled: Cohort 1 — First-line metastatic/advanced pancreatic cancer treated with pela plus atezo and chemotherapy (gemcitabine and nab-paclitaxel) (N=12); Cohort 2 — First-line MSI-H/dMMR metastatic CRC treated with pela plus atezo (N=19); Cohort 3 — Third-line metastatic CRC treated with pela plus atezo and chemotherapy (trifluridine/tipiracil) (N=14); and Cohort 4 — Second-line or later advanced squamous cell carcinoma of the anal canal treated with pela plus atezo (N=10). In Cohorts 1 and 3 (chemotherapy-containing cohorts) the first 3-6 patients enrolled comprise a safety run-in. The primary objectives of GOBLET are safety and efficacy measured by the objective response rate (ORR) at week 16. Based on pre-specified response thresholds, any cohort showing a positive ORR signal in Stage 1 may advance to the 2nd Stage and enroll additional patients.

Results: The three safety run-in patients in Cohorts 1 and 3 have been enrolled and their safety data reviewed by the independent Data Safety Monitoring Board (DSMB). The DSMB identified no safety signal and recommended that enrollment into these cohort continue without modification. Enrollment into Cohorts 2 and 4 is ongoing as these cohorts do not include safety run-ins. Tumor response results to date indicate that two of the three Cohort 1 patients had a partial response at week 8, the third Cohort 1 patient had a partial response at week 16.

Conclusions: No safety signal was observed in either the Cohort 1 (first-line pancreatic cancer) or Cohort 3 (third-line CRC) patients. This is consistent with the favorable safety profile observed in prior studies of pela in multiple cancer indications, and it supports the ability to safely treat patients with advanced GI cancers using pela in combination with checkpoint inhibitors and chemotherapy. Preliminary tumor responses to therapy in first-line pancreatic cancer patients are encouraging.

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P-50 RETRO-TAS, a retrospective observational study of rifluridine/tipiracil in chemorefractory metastatic colorectal cancer

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Background: Trifluridine/tipiracil (TAS-102) is an oral combination of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride, indicated for patients (pts) with metastatic colorectal cancer (mCRC) as third line therapy. The approved dose of TAS-102 in adults is 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs. We conducted an investigator initiated retrospective analysis in patients with chemorefractory mCRC treated with TAS-102 to record clinical practice and to collect real world data on the clinical efficacy of TAS-102 in the Greek population.

Methods: Clinicopathologic characteristics of patients treated in 8 Cancer Centres were collected to assess physician's choice of treatment in chemoresistant mCRC with TAS-102 in third line and beyond. In addition, the clinicopathologic features related to mCRC (focus on molecular profile), duration of treatment, dose modification and toxicity were analysed. The PFS, the OS, the 6-/8-month PFS rate and the disease control rate were calculated. Prognostic factors were evaluated by Cox regression model and Kaplan-Meier curves, along with log-rank tests using Stata/MP 16.0 for Windows.

Results: From October 2018 to October 2021, 200 patients with a median age at diagnosis of 63.7 years (IQR 54.2, 72.1) and at TAS-102 treatment initiation was 67.0 (IQR 58.0, 75.0). At the time of the analysis the median follow-up time was 14 months (IQR 7, 23), 158 PDs and 106 deaths were recorded. Of all patients 42% were females and 58% were metastatic at diagnosis. Molecular analysis revealed mutations in KRAS (52%), NRAS (5%), HER2 (3.5%), BRAF (3.5%) and MSI (9%). Adjuvant chemotherapy and radical surgery was delivered in 39.5% and 51.5% respectively. TAS-102 was administered as a third (70.5%), fourth (17.0%) or fifth line (12.5%) of therapy. Serious adverse events reported were neutropenia (4pts), anemia (2pts), thrombocytopenia (1pt), diarrhea (1pt), nausea (1 pt) and fatigue (8 pts). Dose reduction, delay of initiation of the next cycle and shorter duration of therapy was reported in 25%, 31% and 14.5% of patients. Patients received TAS-102 as monotherapy (71.5%), in combination with bevacizumab (24.5%) or with an anti-EGFR agent (4.0%). The median duration of TAS-102 therapy was 119.5 days and 81% of patients discontinued therapy due to progressive disease. Objective responses during TAS-102 therapy included 0.5% CR, 25% PR, 20% SD and 47% PD, while 7.5% of patients were not evaluable. The median PFS time was 4.8 and the median OS was 11.4 months. The 6 and the 8-month PFS rate was 41.4% and 31.5% respectively. In the multivariable analysis PS>1 and metastatic disease in the liver and lung were adversely associated with survival whereas tumor sidedness and mutational status were not.

Conclusions: This real-world observational study confirms and adds on the findings of the RECOURSE phase III study in relation to the toxicity and the effectiveness of TAS-102 in all subgroups of patients with chemotherapy refractory mCRC, regardless of mutational status and sidedness.

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Legal entity responsible for the study: The authors.

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P-51 Non-invasive HER2 status diagnosis in gastric cancer using surrogate DNA methylation markers

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Background: Gastric cancer (GC) is the fifth most common and fourth most lethal cancer worldwide. Unlike other cancer types, e.g., lung or breast cancer, very few targeted therapeutics have been developed for GC. HER2 (ERBB2) status is an essential biomarker for guiding the trastuzumab (Herceptin) therapy, which is the only molecularly targeted drug accepted as a first-line therapy, for the treatment of patients with advanced HER2-overexpressing GC. HER2 detection in GC often requires repeated testing to improve the accuracy of the result due to its high degree of

heterogeneity. Moreover, HER2 status is dynamic during the clinical course due to genetic differentiation accompanied by neoplastic progression and clonal selection via various factors including chemo- and radiotherapies. Thus, the assessment of HER2 gene copy number in liquid biopsy recently gained a lot of interest for its non-invasiveness, suitability for repeat testing and homogeneity compared to tissue biopsy; however, the limited signal-to-noise ratio (cirdulating tumor DNA (ctDNA) represents a very small fraction in cell-free DNA, which may be less than 0.1%) poses a great challenge for the accuracy and robustness of the tests (either targeted sequencing or droplet digital PCR).

Methods: Targeted bisulfite sequencing using an enriched panel with pre-selected GC-associated CpG sites was performed on 74 FFPE tissue samples (44 IHC0/1+ and 30 IHC3+) to identify HER2-overexpression-specific methylation markers. Then we verified the performance of these markers for HER2 status determination using methylation-specific quantitative PCR (qMSP) in 71 independent tissue samples, as well as three GC cell lines (N-87 and MKN-7 (Her2+), and MKN-28 (Her2-)). We further validated the performance of the markers on 110 GC plasma samples collected before surgery. A HER2-status diagnostic model was built and the performance was evaluated.

Results: We first discovered 105 statistically significant methylation markers for inferring HER2 status in tissue based on the results from targeted sequencing. 69 out of the 105 markers (66%) are located in chromosome 17. qMSP assays were designed for these candidate markers and validated on 110 GC plasma samples. A 3-marker diagnostic model was built and demonstrated sensitivity of 86.7% and specificity of 96.9%, which discriminates HER2-positive from HER2-negative GC patients. The overall plasma-tissue concordance of this liquid biopsy test was 95.5%. Furthermore, the HER2-status test can stratify HER2 IHC2+ patients into either HER2-negative or HER2-positive status, which was confirmed by conventional FISH test.

Conclusions: We have developed a novel, accurate and noninvasive qMSP test for determining HER2 status in GC patients. The high concordance with IHC/FISH results of this blood test holds great promise as an auxiliary method to guide HER2-targeted therapy in GC patients.

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P-52 FOLFIRI or FOLFOX in second line of advanced biliary tract cancer: A retrospective analysis

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Background: Cholangiocarcinoma (CCA) are rare malignancies, globally accounting for 3% of upper gastrointestinal cancer. Despite recent advances in first-line treatment leading to gains in progression-free survival (PFS) and overall survival (OS) with the association of immunotherapy, further lines of treatment are yet underrepresented in large randomized clinical trials. Most robust data in second line treatment is a phase 3 randomized trial ABC06, which has established 5-Fluorouracil and Oxaliplatin (FOLFOX) versus active symptom control, as the best treatment option.

Methods: Single center retrospective study of metastatic or irresectable CCA treated with Cisplatin and Gemcitabine in first-line setting, further exposed to second line treatment with 5-Fluorouracil and Irinotecan (FOLFIRI) or FOLFOX. Primary endpoint was OS and secondary endpoints included PFS and toxicity analysis. OS time was analyzed using the Kaplan-Meier method and differences in survival outcomes were assessed using the log-rank test. Prognostic factors were assessed using univariate and multivariate Cox analysis. A p value < 0.05 was considered significant.

Results: From November 2020 to December 2021 103 patients in first-line setting with Gemcitabine and Cisplatin were included at the study database. Among these, 67 (65%) patients received a second line treatment after disease progression, of which 25 (29.9%) received FOLFIRI and 26 (38.8%) received FOLFOX. Median of treatment cycles was 5 (Interquartile Range [IQR] 2 — 8) in FOLFOX group and 4 (IQR 2 — 9) in FOLFIRI group. Grades 3 and 4 adverse events were no difference between the group FOLFOX (n= 16; 61.5%) vs FOLFIRI (n=14; 56%, p= 0.688). In a median follow up time of 45.5 months, the unadjusted median OS was 8 months (95% confidence interval [CI] 3.31 — 12.68) in FOLFIRI group versus (vs) 5 months (95% CI 0.68 — 9.32; p= 0.259) in FOLFOX group. In Cox's analysis for OS, platinum resistant/refractory chemotherapy had a worse outcome with Hazard Ratio 2.58 (IC 95% 1.35 — 4.92) p= 0.004.

Conclusions: Despite the limitations of retrospective single center study, analysis shows that FOLFIRI may be a safe second-line treatment for metastatic cholangiocarcinoma.

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P-53 A phase 2, multi-center, open-label study of cinrebafusp alfa (PRS-343) in patients with HER2-high and HER2-low gastric or gastroesophageal junction (GEJ) adenocarcinoma

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Background: For patients (pts) with HER2-overexpressing metastatic gastric cancer, trastuzumab + chemotherapy +/- pembrolizumab is a standard first-line option but only provides an incremental overall survival (OS) benefit vs chemotherapy. Anticalin® proteins are recombinant human proteins based on lipocalins. Cinrebafusp alfa, a first-in-class bispecific antibody-Anticalin fusion protein, targets HER2 and the co-stimulatory immune receptor 4-1BB on T cells. In a previous phase 1 study cinrebafusp alfa monotherapy was generally well tolerated and showed deep and durable responses in patients with HER2-positive gastrointestinal malignancies at doses of 8mg/kg Q2W and 18mg/kg Q2W. Significant induction of plasma 4-1BB as well as increase of CD8+ cells was observed in on-treatment tumor biopsies at active dose levels (Piha-Paul, SITC 2020). Based on pharmacokinetics (PK), pharmacodynamics (PD) and clinical efficacy data, a phase 2 dose of 18mg/kg Q2W in C1 followed by 8mg/kg Q2W maintenance was chosen.

Trial design: This is a global, open-label, multicenter, two-arm phase 2 trial of cinrebafusp alfa in patients with metastatic gastric or gastroesophageal junction cancer. Arm 1 is enrolling patients with HER2 high (Immunohistochemistry (ICH) 3+ or IHC 2+ with HER2/neu gene amplification) disease. Pts who have received one prior treatment regimen for metastatic disease, including HER2-directed therapy such as trastuzumab are eligible. Pts will receive cinrebafusp alfa in combination with ramucirumab and paclitaxel. Arm2 is enrolling patients with HER2 low (IHC 1+ or 2+ without HER2/neu gene amplification) disease. Pts who have received at least one prior treatment regimen for metastatic disease are eligible. Pts will receive cinrebafusp alfa in combination with tucatinib. After a run-in consisting of 3 pts in each arm, an additional 17 patients will be enrolled in each arm. For Arm 1, an additional 40 patients may be enrolled after a futility analysis has been conducted. Treatment will continue until disease progression, unacceptable toxicity, or consent withdrawal. Primary endpoint is confirmed overall response rate per RECIST 1.1 and key secondary endpoints are duration of response, progression free survival, overall survival, safety, PK, and immunogenicity. Recruitment is ongoing. Approximately 10 sites in 3 countries in US, Asia and Europe are expected to participate.

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