Pelareorep combined with atezolizumab and chemotherapy demonstrates encouraging results as first-line treatment in advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) patients – Interim results from the GOBLET study

Dirk Arnold [1], Maike Collienne [1], Alexander Stein [2], Guy Ungerechts [3], Eray Goekkurt [2], Jack Chater [4], Houra Loghmani [5], Matt Coffey [5], Richard Trauger [6], Uwe M. Martens [7], Thomas Heineman [6]

Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany[1], Hematology-Oncology Practice Eppendorf (HOPE),Hamburg, Germany[2], University Hospital Heidelberg, Germany[3], Klinikum Chemnitz gGmbH, Germany[4], Oncolytics Biotech Inc., Calgary, Canada[5], SLK-Kliniken Heilbronn GmbH, Heilbronn, Germany[7], Oncolytics Biotech Inc, San Diego, USA[6]

SITC 2022, Abstract ID: 650

Background and Study Design

Pelareorep (pela) is an intravenously administered, naturally occurring, non-genetically modified reovirus. Pela selectively kills tumor cells and promotes tumor-directed innate and adaptive immune responses resulting in increased T cell infiltration and PD-L1 expression in tumors, thereby priming the tumor for checkpoint blockade therapy [1] (Fig 1).

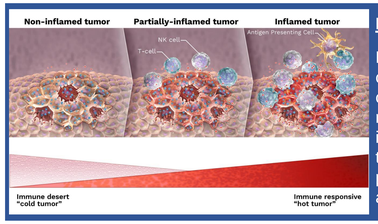


Figure 1: Pelareorep's mechanism of action

Pelareorep selectively infects and lyses cancer cells. In addition, it delivers dsRNA to cancer cells that is detected by pattern recognition receptors leading to the expression of interferons and inflammatory cytokines. This, in turn, results in immune cell recruitment and promotes the development anti-tumor innate and adaptive immune response.

GOBLET is an open-label, multiple-cohort, phase 1/2, Simon 2-stage study to assess the safety and efficacy of pela in combination with atezolizumab (atezo) +/- chemotherapy in 4 different gastrointestinal cancer indications (Fig 2). We hypothesize that treatment with pela will prime the tumor microenvironment for checkpoint blockade therapy by increasing PD-L1 expression, stimulating the generation of new T cell clones, and facilitating immune cell infiltration into the tumor. GOBLET is currently ongoing. Here we report interim results for patients with advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) (Cohort 1; data cut-off October 12, 2022).

Primary Objectives:

- To evaluate Objective Response Rate (ORR) at Week 16
- To evaluate tolerability of the investigational therapy

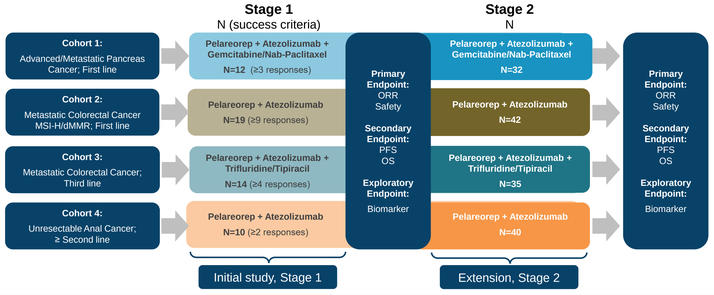
Secondary Objective:

- To assess other efficacy metrics including overall ORR, progression-free survival (PFS) and overall survival (OS)

Exploratory Objective:

- To evaluate the immunological changes within tumor tissue and peripheral blood and to examine potential biomarkers of response to treatment

Figure 2: GOBLET study design



Methods

GOBLET is a phase 1/2 Simon two-stage study. PDAC patients enrolled in GOBLET are treated with pela ($4.5x10^{10}$ $TCID_{50}$, days 1,2; 8,9 and 15,16), atezolizumab (840 mg, days 3 and 17), and gemcitabine (1000 mg/m^2)/nab-paclitaxel (125 mg/m^2) on days 1, 8 and 15. They must have locally advanced or metastatic unresectable disease evaluable by RECIST v1.1, be ≥18 years old, and have an ECOG score ≤1. No previous checkpoint inhibitor treatment is permitted. Target enrollment for Stage 1 is 12 evaluable PDAC patients (evaluable patients must have at least one post-baseline tumor assessment). The protocol-specified Stage 1 success criterion for PDAC is ≥3 confirmed responses. In addition, blood samples collected at baseline (cycle 1 day 1 [c1d1]) and c2d1 of the 28-day treatment cycle will undergo T cell receptor sequencing (TCR-seq) to assess treatment effects on the T cell repertoire.

Results - Demographics and Safety

Data from the 3-patient safety run-in were reviewed by DSMB and German regulatory authorities, and no safety concerns were noted. Therefore, the study opened for full enrollment without modifications. To date, the treatment combination has been well tolerated with no safety concerns. The most frequently (>3 patients) reported treatment emergent adverse events (TEAEs) are listed in Table 1, and the profiles of evaluable patients are listed in Table 2:

Table 1: Most frequent (>3 patients) AEs

Adverse Events (MedDRA preferred terms)	All TEAEs N=18, n (%)	Grade 3/4 TEAEs N=18, n (%)
Pyrexia	11 (61%)	0 (0%)
Thrombocytopenia	7 (39%)	0 (0%)
Chills	6 (33%)	0 (0%)
Fatigue	5 (28%)	0 (0%)
Anemia	5 (28%)	1 (6%)
Nausea	5 (28%)	0 (0%)
Diarrhea	5 (28%)	0 (0%)
Neutropenia	4 (22%)	3 (17%)
Hypotension	4 (22%)	0 (0%)
Lymphocyte count decreased	3 (17%)	1 (6%)
ALT decreased	3 (17%)	0 (0%)
Neutrophil count decreased	3 (17%)	2 (11%)
Leukopenia	3 (17%)	1 (6%)
Dyspnea	3 (17%)	1 (6%)
Epistaxis	3 (17%)	0 (0%)
Alopecia	3 (17%)	0 (0%)

Table 2: Profiles of evaluable patients

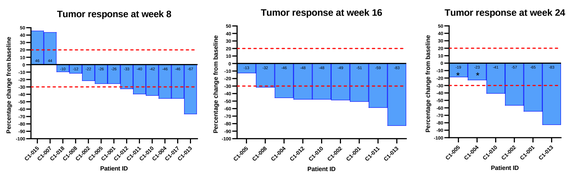
Patient #	Age (years)	Sex	ECOG score	Metastases (location)	Target lesion size at baseline (mm)
C1-001	72	F	1	None	65
C1-002	54	M	1	Peritoneum	37
C1-004	63	F	1	Lung	13
C1-005	71	M	0	Liver	79.5
C1-007	54	M	0	Liver	63
C1-008	53	M	0	Liver	187
C1-010	67	M	0	Liver	39.1
C1-011	69	M	0	Liver	15.7
C1-012	49	M	0	Liver	52.1
C1-013	65	M	1	Lymph node	30
C1-015	71	M	0	Liver	24
C1-017	76	F	0	Liver	56
C1-018	54	M	0	Peritoneum	29
C1-019	54	M	0	Liver	39
	Ave: 62.3 yrs	79% male	71% ECOG 0 29% ECOG 1	93%: mets 64%: liver mets	Ave: 52 mm

Results - Tumor response at Weeks 8, 16 and 24

Of the 13 evaluable patients at Week 8, 6 patients had PR, 5 had SD, and 2 had PD. Of the 9 evaluable patients at Week 16, 1 had CR, 7 had PR, and 1 had SD. Of the 6 evaluable patients at Week 24, 1 had CR, 3 had PR, and 2 had PD.

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease

Figure 4: Tumor response at Week 8, 16 and 24



Numbers indicate the percent change in target lesion size from baseline. Dotted lines represent cut-offs for progressive disease (+20%) or partial response (-30%). Patient C1-013 was reported as a CR at Week 16 and Week 24.

* Progressive disease per RECIST v1.1.

Results - Tumor responses over time

Figure 4: Response to treatment over time (evaluable or potentially evaluable patients)

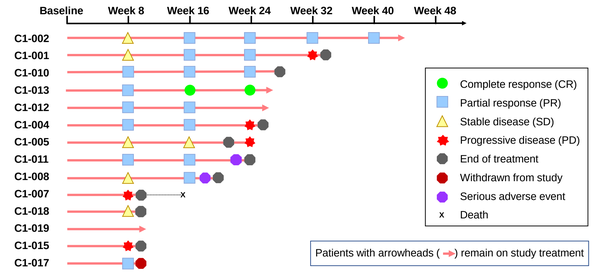


Figure 5: Tumor images for patient C1-013

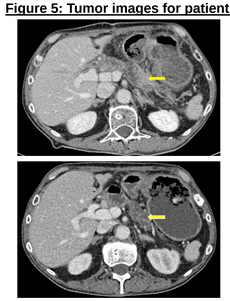
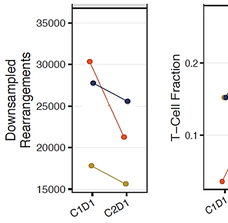


Fig 4. Best responses for the 13 evaluable patients at cut-off date: CR=1, PR=8, SD=2 and PD=2. Of the 9 patients with CR or PR, 7 responses were confirmed by a subsequent scan. ORR and clinical benefit rate (CBR) are 69% and 85%, respectively. **Fig 5.** Baseline and Week 24 scans for patient C1-013. Longest tumor diameter decreased from 30 mm at baseline to too small to measure at Week 24. ORR=CR+PR/total patients; CBR=CR+PR+SD/total patients

Results - TCR Sequencing

- TCR-sequencing results are available for 3 patients. These demonstrated a decrease in diversity (down-sampled re-arrangements) consistent with expansion of mid-frequency clones. Diversity was calculated as the number of unique productive rearrangements after computationally down-sampling to a common number of T cells. Lower values in diversity are associated with more expanded clones (Fig 6, left).
- All 3 patients showed an increased T cell fraction following treatment. Higher T cell fraction has been associated with better outcomes in IO studies[2] (Fig 6, right).

Figure 6: TCR seq. results



Conclusions

- The PDAC cohort (Cohort 1) of the GOBLET study has exceeded the protocol-specified success criterion of ≥3/12 objective responses for Stage 1
- The ORR of 69% in PDAC patients treated with pelareorep + atezolizumab + chemotherapy is substantially higher than historical response rates (ORR~25%)[3] reported for PDAC patients treated with gemcitabine/nab-paclitaxel in earlier phase 3 studies
- The treatment combination was well tolerated, and the observed AE profile is consistent with the favorable safety profile observed in prior pelareorep studies with or without chemotherapy

Given the strong efficacy signal observed in this study, the combination of pelareorep, atezolizumab and gemcitabine/nab-paclitaxel warrants further evaluation in patients with metastatic pancreatic cancer.

Eudra-CT #:2020-003996-16 **Coordinating Investigator:** Dirk Arnold **Contact:** akupic@oncolytics.ca & Matthias.Lendner@aio-studien-ggmbh.de

Ref: 1) Samson et al. (2018) 2) Bentham, R et al. Nature 597, 555–560 (2021) 3) Von Hoff, et al., NEJM 2013