Pelareorep (pela) + atezolizumab (atezo) and chemotherapy in first-line (1L) advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) patients – Results from the GOBLET study

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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 (Samson et al., 2018) (Fig 1).

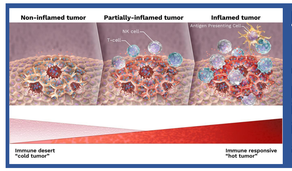


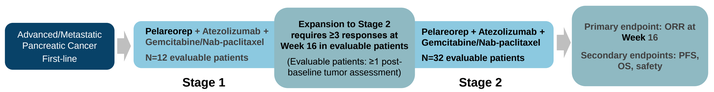
Figure 1: Pelareorep's mechanism of action.

Pelareorep selectively infects cancer cells leading to tumor cell lysis. In addition, its dsRNA genome is identified 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 different GI cancers. Here we report the updated results for patients with pancreatic ductal adenocarcinoma (PDAC).

Hypothesis: Pela primes the tumor microenvironment for checkpoint blockade therapy by increasing PD-L1 expression, promoting T cell expansion, and facilitating immune cell infiltration into the tumor.

Figure 2: Study Design & Methods: (only PDAC cohort shown)



Primary Objectives:

- Objective Response Rate (ORR) at Week 16
- Tolerability of the pela-based combination therapy

Secondary Objectives:

- Progression-free survival (PFS) and overall survival (OS)

Exploratory Objectives:

- To evaluate the immunologic effects of treatment and to explore potential biomarkers of treatment response

PDAC patients were treated with pela ($4.5x10^{10}$ $TCID_{50}$ on days 1,2; 8,9 and 15,16), atezo (840 mg on days 3 and 17), and gemcitabine (1000 mg/m^2)/nab-paclitaxel (125 mg/m^2) on days 1, 8 and 15. Patients must have unresectable locally advanced or metastatic PDAC evaluable by RECIST v1.1, be ≥18 years old, and have an ECOG score ≤1.

The protocol-specified Stage 1 success criterion is ≥3 confirmed responses.

Blood samples and pretreatment tumor samples were collected for translational analyses including T cell receptor sequencing (TCR-seq).

Results – Safety and Patient Characteristics

A 3-patient safety run-in was completed, and no safety concerns were noted by the Data Safety Monitoring Board.

The treatment has been well-tolerated with no safety concerns. The most frequently reported (≥4 patients) treatment emergent adverse events (TEAEs) and Grade 3 & 4 TEAEs are listed in Table 1. There were no fatal events associated with the investigational agents.

Patients were 85% male with and average age of 61.2 years (range: 49-72). ECOG scores were 0 (31%) and 1 (69%). 93% of patients had metastatic disease and 69% had liver metastases.

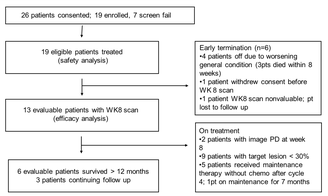
Table 1: Most frequent (≥4) and treatment-emergent adverse events

Adverse Event (MedDRA Preferred Term)	All TEAEs N=19, n (%)	Grade 3/4 TEAEs N=19, n (%)
Pyrexia	15 (78.9%)	1 (5.3%)
Anaemia	12 (63.2%)	4 (21.1%)
Chills	10 (52.6%)	0 (0.0%)
Fatigue	10 (52.6%)	2 (10.5%)
Thrombocytopenia	8 (42.1%)	1 (5.3%)
Nausea	7 (36.8%)	0 (0.0%)
Platelet count decreased	6 (31.6%)	1 (5.3%)
Neutrophil count decreased	6 (31.6%)	5 (26.3%)
Urinary tract infection	6 (31.6%)	2 (10.5%)
Alanine aminotransferase increased	5 (26.3%)	0 (0.0%)
Diarrhoea	5 (26.3%)	1 (5.3%)
Dyspnoea	5 (26.3%)	1 (5.3%)
Hypertension	5 (26.3%)	2 (10.5%)
Leukopenia	5 (26.3%)	2 (10.5%)
Neutropenia	5 (26.3%)	3 (15.8%)
Oedema peripheral	5 (26.3%)	1 (5.3%)
Alopecia	4 (21.1%)	0 (0.0%)
Aspartate aminotransferase increased	4 (21.1%)	0 (0.0%)
Hypotension	4 (21.1%)	0 (0.0%)

Results - Tumor response over time, PFS and OS

From Oct. 2021 to Aug. 2022, 13 evaluable PDAC patients were enrolled. Response results for these patients are shown below.

Figure 3a: Patient enrolment flowchart



Overall ORR: 62%

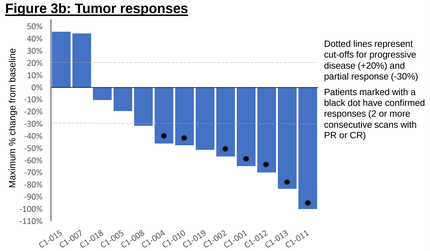
Confirmed ORR: 54% (confirmed response: ≥2 consecutive evaluations showing a response)

Disease control rate (DCR): 85%; median duration of response (DOR): 5.7 months

The interim 12-month survival rate: 46%

Note: 12-mo survival rate and mOS are not mature as patients continue to be followed for survival

Figure 3b: Tumor responses



Dotted lines represent cut-offs for progressive disease (+20%) and partial response (-30%)

Patients marked with a black dot have confirmed responses (2 or more consecutive scans with PR or CR)

Figure 4: Tumor responses over time

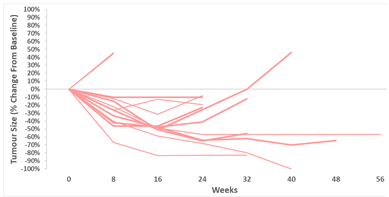


Figure 5: PFS and OS

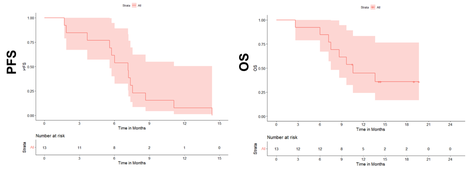


Table 2: PFS and OS summary

N	Events	Median PFS	0.95 LCL	0.95 UCL
13	13	7.2	5.6	NA
N	**Events**	**Median OS***	**0.95 LCL**	**0.95 UCL**
13	8	10.6	7.5	NA

* OS not mature as patients remain in follow-up

CR = complete response; PR = partial response; SD = stable disease

ORR = Objective response rate (CR+PR / total patients)

CBR = Clinical benefit rate (CR+PR+SD / total patients)

Results – TCR Sequencing (TCR-seq)

Analysis of changes in peripheral blood T cell clonal populations pre- and post-treatment showed an expansion of both new and pre-existing T cell clones. New clonal expansion is consistent with the generation of an anti-viral T cell response (Fig 6a).

At baseline, tumors had a mean of 22% tumor infiltrating lymphocytes (TILs) by T cell fraction. Simpson clonality of baseline TILs ranged from 1% to 11% and did not appear to predict pela-induced TIL expansion in the blood or clinical response (Fig 6b).

TCR-seq analysis of blood revealed expansion of TIL-specific clones. Study treatment led to the expansion in the blood of both pre-existing TIL clones and new TIL clones not found at baseline (Fig 6c).

The largest increase in TIL clone expansion was between Cycles 2 and 4. **Subjects with increased blood TILs showed a decrease in tumor size** (Fig 6d).

Figure 6a: Treatment-induced changes in blood T cell populations

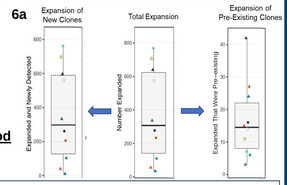


Figure 6b: Tumor infiltrating T cells – fraction and clonality

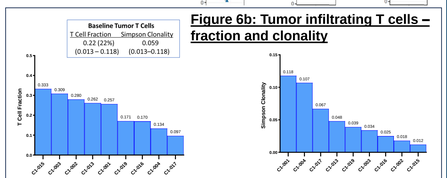


Figure 6c: Expansion of TIL-specific clones in the blood

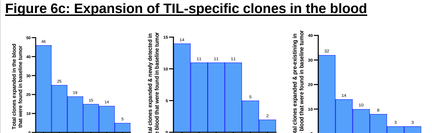
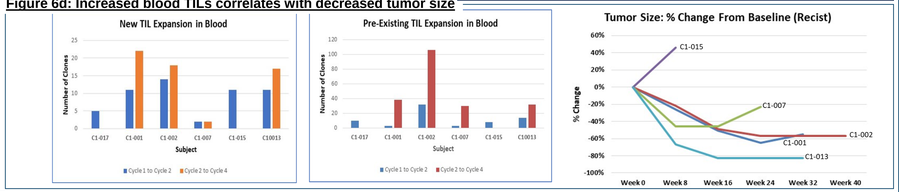


Figure 6d: Increased blood TILs correlates with decreased tumor size



Conclusions

- The study treatment combination, pela, atezo and gemcitabine/nab-paclitaxel, resulted in tumor responses greatly surpassing historical outcomes (Von Hoff, et al., NEJM 2013) in 1L PDAC patients: 62% overall ORR, with a confirmed ORR of 54% and a DCR of 85%.
- The study yielded encouraging PFS, OS, and 12-month survival rates.
- The treatment combination was well tolerated.
- Translational results support pela's immunologic mechanism of action:
  - Study treatment resulted in the expansion of T cell clones in the blood, including both pre-existing and new TIL-specific clones.
  - Expansion of TIL clones appears to correlate with tumor response.
- Pela, atezo, and gemcitabine/nab-paclitaxel will be evaluated as an arm in the Ph3 Precision Promise study. In addition, the novel combination of mFOLFIRINOX + pela +/- atezo will be investigated as a new arm in the GOBLET study.

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