Results of the Safety Run-in for First-line Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) Patients Treated with Pelareorep + Modified FOLFIRINOX +/- Atezolizumab

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Background

- **GOBLET is a platform study designed to assess pelareorep (pela) combined with checkpoint inhibitors (CPIs), +/- chemotherapy, in GI cancers.**
- Immunotherapies are effective in only the small subset of metastatic PDAC patients with microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR) tumors. However, prior data suggest pelareorep may synergize with CPIs to benefit patients with GI cancers. In particular, pela combined with gemcitabine/nab-paclitaxel + atezolizumab (Tecentriq®) previously showed promising tumor response rates in metastatic PDAC and second-line anal cancer.
- Pela is a non-genetically modified, intravenously administered reovirus that selectively replicates in cancer cells. Pela's anticancer activity primarily results from its immunologic effects:
  1. Pela stimulates tumor-specific adaptive immune responses including the expansion of pre-existing tumor-infiltrating lymphocyte (TIL) clones.
  2. Pela remodels the tumor microenvironment (TME) to make it more visible to the immune system. This includes upregulating expression of interferon-γ and interferon-α-induced genes such as PD-L1, CXCL9, CXCL10, and CXCL11.
  3. PD-L1 upregulation also provides a basis for synergy between pela and immune checkpoint inhibitors.
- **This cohort of the GOBLET study evaluates the safety and efficacy of pela combined with modified FOLFIRINOX, +/- atezolizumab, as first-line therapy in metastatic mPDAC. Here, we present the results of the safety run-in.**

Pelareorep Mechanism of Action

Pela induces anticancer adaptive immune responses and an inflammatory TME:

- Stimulates expansion of TIL clonal populations
- Pela's double-stranded RNA induces interferon-regulated gene expression, e.g., CXCL9, CXCL10, CXCL11 and PD-L1
- Consequently, pela-treated tumors are visible to the immune system as evidenced by increased T cell infiltration into tumors
- Upregulation of PD-L1 also provides a basis for synergy with checkpoint inhibitors

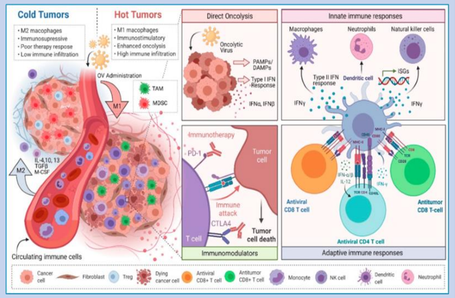
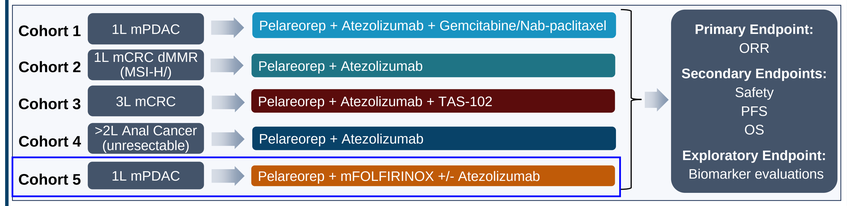


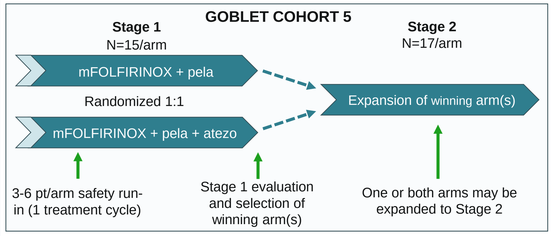
Fig. from Viruses 2021, 13, 654

Study Design and Objectives

GOBLET Study Overview (Eudra-CT: 2020-003996-16):



- GOBLET is an open-label, multiple-cohort, phase 1/2, Simon 2-stage study of pela-based combination therapies in patients with advanced or metastatic GI cancers.
- Cohort 5 is currently enrolling patients with mPDAC according to the design, below:



Design	Phase 1/2 randomized Simon two-stage
Population	Newly diagnosed mPDAC with measurable lesions by RECIST v1.1
Treatment	28-day cycles: • Pela: Days 1,2, 8,9, 15,16 • mFOLFIRINOX: Days 1,15 • Atezo: Days 2,16

Study Objectives:

Primary:

1) Safety and tolerability of pelareorep + mFOLFIRINOX with or without atezolizumab
2) Efficacy based on objective response rate (ORR)

Secondary: Progression-free survival, overall survival, 12- and 24-month survival rates, duration of response, disease control rate

Exploratory: TIL clonal expansion and other immunological changes in blood and tumor

Translational studies include:

- TCR sequencing to evaluate TIL clonal expansion
- Inflammatory responses to treatment
- Circulating tumor cells/DNA
- Correlation of tumor responses to immune markers

Key Inclusion Criteria:

1) 18 years or older with confirmed mPDAC eligible for treatment with mFOLFIRINOX
2) No prior systemic chemotherapy for mPDAC or >6 months after last dose of adjuvant chemotherapy
3) ECOG performance status of 0 or 1
4) Radiographically measurable disease as defined by RECIST v1.1
5) Adequate organ function including AST/ALT/GGT ≤2.5 x ULN (≤5 x ULN if liver metastases)
6) No previous treatment with checkpoint inhibitors
7) Known low or absent dihydropyridine dehydrogenase (DPD) activity

Results

Safety results (overall population)**:**

- Nine patients have been treated
  - Six were considered part of the per protocol the safety run-in
- AEs:
  - All patients experienced at least one AE
  - Most common AEs (>2 patients): diarrhea, nausea, pyrexia, abdominal. pain, constipation, vomiting, anemia, fatigue, γ-GGT elevation, hypocalcemia, hypokalemia
  - Seven patients had ≥ Grade 3 AE (3 in Arm A; 4 in Arm B)
  - Three Grade 3 or higher AEs occurred in ≥2 or more patients (Table 1)
- Serious AEs:
  - Six patients had an SAE: 2 in Arm A, 4 in Arm B (Table 2)
- Deaths
  - Three deaths occurred after data cut-off (Causes: progressive disease; kidney failure + progressive disease; unknown)
  - None were considered treatment related

Table 1. Grade 3 or higher AEs (≥2 in all patients)

MedDRA Preferred Term	ARM A (Pela/mFOLFIRINOX/ Atezolizumab) N = 4 (%)	ARM B (Pela/mFOLFIRINOX) N = 5 (%)	Total (Arm A & Arm B) N = 9 (%)
Nausea	1 (25.0%)	3 (60.0%)	4 (44.4%)
γ-GGT increased	1 (25.0%)	1 (20%)	2 (22.2%)
Abdominal pain	0 (0.0%)	2 (40.0%)	2 (22.2%)

Table 2. Serious AEs (all patients)

MedDRA Preferred Term	ARM A (Pela/mFOLFIRINOX/ Atezolizumab) N = 4 (%)	ARM B (Pela/mFOLFIRINOX) N = 5 (%)	Total (Arm A & Arm B) N = 9 (%)
Nausea	0 (0.0%)	2 (40.0%)	2 (22.2%)
Abdominal pain	0 (0.0%)	1 (20%)	1 (11.1%)
Acute kidney injury	1 (25.0%)	0 (0.0%)	1 (11.1%)
COVID-19	0 (0.0%)	1 (20%)	1 (20%)
Diarrhea	1 (25.0%)	0 (0.0%)	1 (11.1%)
Fatigue	0 (0.0%)	1 (20%)	1 (11.1%)
General health deterioration	0 (0.0%)	1 (20%)	1 (11.1%)
Hypophysitis	1 (25.0%)	0 (0.0%)	1 (11.1%)
Ileus	0 (0.0%)	1 (20%)	1 (11.1%)
Infection	0 (0.0%)	1 (20%)	1 (11.1%)
Infusion reaction	1 (25.0%)	0 (0.0%)	1 (11.1%)
Pulmonary embolism	0 (0.0%)	1 (20%)	1 (11.1%)
Vomiting	0 (0.0%)	1 (20%)	1 (11.1%)

Conclusions

- No safety signals were observed in newly diagnosed mPDAC patients treated with pela + mFOLFIRINOX +/- atezolizumab after 1 treatment cycle (safety run-in period)
- Observed AEs were consistent with the known safety profiles of the study drugs
- An independent DSMB and the German regulatory authorities have approved the study to continue full enrollment
- Safety of these combination therapies will continue to be monitored
- Tumor response results to pela + mFOLFIRINOX +/- atezolizumab therapy are pending

Enrollment into Cohort 5 of the GOBLET study will continue – Efficacy results will be reported when available