Phase 1/2 Randomized, Open-label, Multicenter, Simon Two-stage Study of Pelareorep Combined with Modified FOLFIRINOX +/- Atezolizumab in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

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Background

Pancreatic ductal adenocarcinoma (PDAC) is the 3rd leading cause of cancer deaths in the US. Cytotoxic chemotherapy remains the standard of care for most metastatic PDAC (mPDAC) patients.

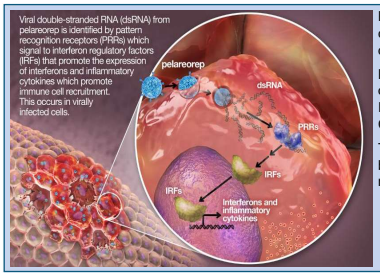
Immune-based therapies have not yet proven beneficial for the large majority of PDAC patients, presumably due to the immunologically "cold" nature of the tumor. In most patients, $CD8^+$ T cell infiltration into the tumor is limited, and the tumor microenvironment (TME) contains suppressive cell populations such as myeloid-derived suppressor cells, regulatory T cells, and tumor-associated macrophages. In addition, the distinctive desmoplastic stroma found in PDAC tumors may contribute to immunosuppression within the TME.

Pelareorep (pela) is a naturally occurring, non-genetically modified reovirus that selectively infects cancer cells following intravenous administration. Upon infection of cancer cells, pela's double-stranded RNA genome stimulates a proinflammatory response that primes tumors for immunologic killing. This includes increased T cell infiltration into tumors and stimulation of innate and adaptive immune responses characterized by the expansion of tumor-infiltrating lymphocyte (TIL) clones.

Pela combined with chemotherapy, checkpoint inhibitors, or both has shown promising efficacy in several malignancies, including mPDAC:

- In mPDAC, first-line treatment with pela combined with gemcitabine/nab-paclitaxel and the PD-L1 inhibitor atezolizumab yielded a 62% objective response rate (ORR)

Pela promotes a pro-inflammatory TME and the development of both innate and adaptive immune responses:



Pela selectively infects cancer cells leading to accumulation of dsRNA

Pela dsRNA enhances expression of genes regulated by IFN-α and IFN-γ including CXCL9, CXCL10, CXCL11, PD-L1, and many others

This results in the development of both innate and adaptive immune responses including:

- Activation of natural killer (NK) and dendritic cells
- Expansion of tumor infiltrating lymphocyte (TIL) clones

The current study is designed to evaluate the safety and efficacy of pelareorep plus modified FOLFIRINOX (mFOLFIRINOX), with or without atezolizumab, as first-line therapy in patients with mPDAC

Study Design and Objectives

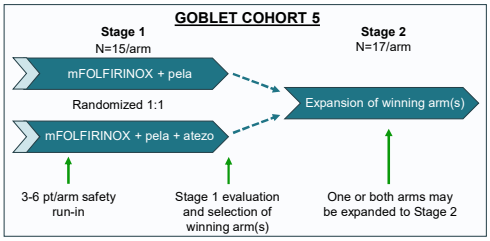
The current study is being conducted as a new cohort (Cohort 5) in the ongoing GOBLET platform study. GOBLET is an open-label, multiple-cohort, phase 1/2 study of pela-based combination therapies in patients with advanced or metastatic GI cancers.

GOBLET Study Overview:

- **Primary Objectives:**
  1) Safety and tolerability of pelareorep + mFOLFIRINOX with or without atezolizumab
  2) Efficacy based on objective response rate (ORR) per RECIST v1.1
- **Secondary Objectives:** Efficacy based on progression-free survival, overall survival, 12- and 24-month survival rates, duration of response, disease control rate

GOBELT Study Cohort 5:

Design	Phase 1/2 randomized Simon two-stage screened selection design
Population	Newly diagnosed mPDAC with measurable by RECIST v1.1
Study Arms (Randomized 1:1)	1) Pelareorep + mFOLFIRINOX 2) Pelareorep + mFOLFIRINOX + atezolizumab
Treatment	28-day cycles Pela: Days 1,2,8,9,15,16; mFOLFIRINOX: Days 1,15; Atezo: Days 2,16



Key Inclusion Criteria

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

Key Exclusion Criteria

1) Previous radiotherapy, surgery, chemotherapy, or investigational therapy for of mPDAC
2) Previous treatment with immune checkpoint inhibitors
3) History of allergy or known hypersensitivity to any of the study drugs
4) Known low or absent dihydropyridine dehydrogenase (DPD) activity
5) Active, uncontrolled infections
6) Symptomatic brain metastasis
7) Pregnant or breastfeeding women

Translational Evaluations

Exploratory Objective: To evaluate potential biomarkers and effects of treatment on the TME

- Tumor tissue is being collected at Baseline (fresh or archival) and (optionally) at the end of treatment in Cycle 2
- Blood is being collected at Baseline and on Day 1 of Cycles 2, 4, 6, 8,12
- Planned evaluations include:
  - TCR sequencing to evaluate TIL clonal expansion in the blood
  - Plasma chemokine and cytokine responses to treatment
  - Plasma circulating tumor DNA levels
  - Expression of immune-related biomarkers such as PD-L1
- Correlations to tumor responses will be assessed

GOBLET Study Status

Approximate number of sites: 20 sites in Germany

Protocol Number: Eudra-CT Number: 2020-003996-16

Status: The study is currently recruiting patients

Conducted by: Oncolytics Biotech Inc. in collaboration with AIO-Studien-gGmbH

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