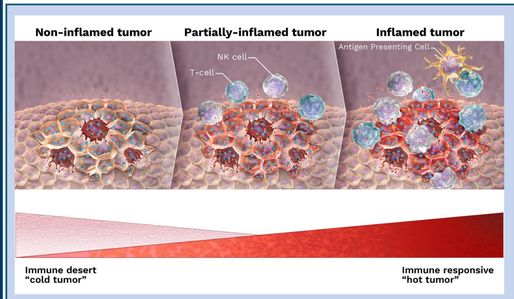
GOBLET: A phase 1 / 2 multiple-indication biomarker, safety, and efficacy study in advanced or metastatic gastrointestinal cancers exploring treatment combinations with pelareorep and atezolizumab

Dirk Arnold[1], Maike Collienne[1], Houra Loghmani[2], Thomas Heineman[3]
Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany[1] Oncolytics Biotech Inc., Calgary, Canada [2] , Oncolytics Biotech Inc, San Diego, USA [3]

Background

- Gastrointestinal (GI) cancers collectively make up 35% of all cancer-related deaths and this number is projected to increase to 73% by 2040 (Ferlay et al., 2020). In the last decade, one emerging treatment option has been the use of immunotherapy with monoclonal antibodies against immune-checkpoint proteins. However, checkpoint blockade inhibitors are beneficial in only a small subset of patients (3.8%) with microsatellite instability-high and deficient mismatch repair (MSI-H/dMMR) tumors, characterized as having a high predisposition for genetic mutations (Bonneville et al., 2017). MSI-H tumors have a less immunosuppressive tumor phenotype, while the microsatellite-stable (MSS) tumors have a "cold" phenotype characterized by fewer mutations, less immune cell infiltration, and immune checkpoint protein downregulation, making them resistant to immunotherapy.

- 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, thereby priming the tumor for checkpoint blockade therapies (Samson et al., 2018).

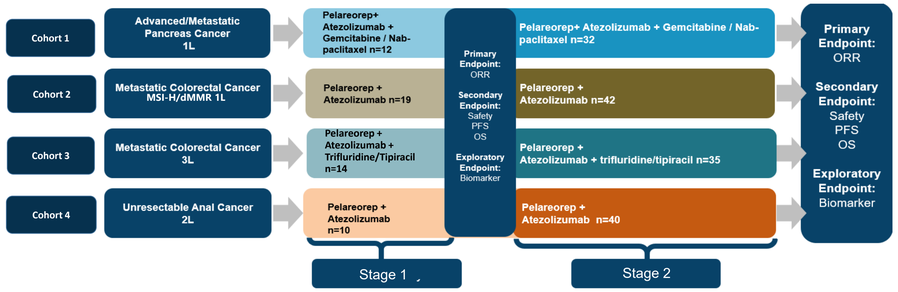


Pelareorep mechanism of action.
Pelareorep selectively infects cancer cells leading to tumor cell lysis. The virus also mediates anti-tumor immunity by activating both innate and adaptive immune response. We hypothesize that pelareorep mediated immune responses will enhance the response to anti-PD-L1 therapy.

- Given the encouraging efficacy signals in prior GI studies with pela, and the potential synergy with checkpoint blockade, the GOBLET study will examine the efficacy of pela plus anti-PD-L1 therapy, atezolizumab, in multiple GI indications. 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, resulting in the enhanced activity of atezolizumab and better clinical outcomes.

Study Design and Objectives

GOBLET is an open-label, non-randomized, multiple-cohort, phase 1/2 study in patients with advanced or metastatic GI cancers. The four cohorts are indicated in the figure below.



Cohort 1: 1st line (1L) locally advanced/metastatic unresectable pancreatic ductal adenocarcinoma
Cohort 2: Metastatic colorectal cancer 1L (MSI-H/dMMR) with no prior systemic treatment for metastatic disease
Cohort 3: Metastatic colorectal cancer patients who failed (and/or did not tolerate) 2 prior lines of treatment and are eligible for 3L standard of care (SOC) chemotherapy with trifluridine/tipiracil
Cohort 4: Locally advanced/metastatic unresectable squamous cell carcinoma of the anal canal (SCCA) of viral (HPV) or non-viral origin in patients who failed (and/or did not tolerate) prior systemic chemotherapy ≥2L

- If a cohort shows a promising objective response rate (ORR) in Stage 1 of the Simon two-stage design, that cohort may be expanded to enroll additional patients in an extension phase (Stage 2).
- The first 3 patients enrolled into Cohort 1 and Cohort 3 will comprise the Phase 1b portion of the study in which the safety of the three-drug combination will be assessed during the first 28-day treatment cycle prior to enrolling additional patients into these cohorts.

Study Objectives

- **Primary Objectives:**
  Efficacy: ORR at week 16
  Safety: To evaluate the tolerability of the combination of pela plus atezolizumab (with or without chemotherapy depending on the cohort)
- **Secondary Objectives:**
  Efficacy: To assess the anti-tumor activity of the treatment combinations based on progression-free survival (PFS) and overall survival (OS)
- **Exploratory Objectives:** To evaluate the immunological changes within tumor tissue and peripheral blood and to examine potential biomarkers of response to treatment

Study Information

Key inclusion criteria

- ✓ 1. Meet the specific diagnostic criteria for each cancer type depending on the cohort.
- ✓ 2. 18 years or older.
- ✓ 3. ECOG performance status of 0 or 1.
- ✓ 4. Evaluable or measurable lesions per RECIST v1.1.
- ✓ 5. Adequate organ function at the time of enrollment.
- ✓ 6. INR ≤1.5 x ULN and PTT or aPTT ≤1.5 x ULN unless receiving treatment with therapeutic anticoagulation.

Key exclusion criteria

- × 1. Systemic chemotherapy, radiotherapy, or surgery <4 weeks before study treatment.
- × 2. Previous treatment with immune checkpoint inhibitors.
- × 3. Autoimmune disease requiring systemic treatment in the past 2 years
- × 4. Acute coronary syndrome, coronary angioplasty or stent placement within 6 months, ≥grade 3 CHF, uncontrolled hypertension.
- × 5. History of pneumonitis requiring steroids or active pneumonitis.
- × 6. Symptomatic brain metastasis.
- × 7. Pregnant or breastfeeding women.
- × 8. HIV infection (patients with controlled HIV eligible for Cohort 4).

GOBLET sites

Center	Location	Investigator
Asklepios Kliniken Hamburg GmbH, Asklepios Tumorzentrum* Abteilung für Onkologie mit Sektion Hämatologie	Hamburg	Prof. Dr. med. Dirk Arnold (LKP)
Klinikum der Universität München-Großhadern, Medizinische Klinik III	München	Prof. Dr. med. Volker Heinemann
Caritasklinikum Saarbrücken St. Theresia*	Saarbrücken	Prof. Dr. med. Manfred Lutz
Hämatologisch-Onkologische Praxis Eppendorf*	Hamburg	Prof. Dr. med. Eray Gökkurt
St. Josef-Hospital, Klinikum der Ruhr-Universität Bochum Abt. für Hämatologie, Onkologie u. Palliativmedizin	Bochum	Prof. Dr. med. Anke Reinacher-Schick
Universitätsklinikum Ulm, Klinik für Innere Medizin	Ulm	Prof. Dr. med. Thomas Seufferlein
Universitätsklinikum Tübingen, Medizinische Klinik* Abteilung Innere Medizin VIII - Medizinische Onkologie und Pneumologie	Tübingen	Prof. Dr. med. Ulrich Lauer
Charité Universitätsklinikum Berlin Campus Virchow, Med Klinik m. S. Hämatologie/Onkologie	Berlin	Prof. Dr. med. Dominik Modest
Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II	Würzburg	Prof. Dr. med. Volker Kunzmann
Klinikum Chemnitz gGmbH	Chemnitz	Jack Chater
Gemeinschaftspraxis Dr. med Bernhard Heinreich / Prof. Markus Bangerter* Innere Medizin, Hämatologie, Onkologie und Medikamentöse Tumortherapie	Augsburg	Dr. med. Bernhard Heinrich
SLK-Kliniken Heilbronn GmbH, Klinik für Innere Medizin III	Heilbronn	Prof. Dr. med Uwe Martens
München Klinik Neuperlach, Klinik für Hämatologie und Onkologie	München	Prof. Dr. med. Meinolf Karthaus
Nationales Centrum für Tumorerkrankungen Heidelberg	Heidelberg	Prof. Dr. med. Dr. rer. nat. Guy Ungerechts

* Sites open to recruitment as of 1Jan22

Protocol Number: Eudra-CT Number: 2020-003996-16
Status: The study is currently recruiting patients. The 3-patient safety run-in recruitment in Cohorts 1 and Cohort 3 have been completed.
Coordinating Investigator: Dirk Arnold, MD, PhD
Study contact information:
akupic@oncolytics.ca and Matthias.Lendner@aio-studien-ggmbh.de