Background

Gastrointestinal (GI) cancers collectively make up 35% of all cancer-related deaths and this number is projected to increase to 73% by 2040 (Farley 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.

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Pelareorep (pela) is an intravenously administered, naturally occurring, mechanism of action. Pelareorep selectively infects cancer cells leading to tumor lysis. The virus also mediates an antitumor immune response by activating both 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 lysis. The virus also mediates an antitumor immune response by activating both 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).

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 care of SOC chemotherapy with trifluoridine/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

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.
7. Pregnant or breastfeeding women.
8. HIV infection (patients with controlled HIV eligible for Cohort 4).