STUDY TYPE	Phase 1/2
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SPONSOR	Oncolytics Biotech, Inc. Suite 804, 322 11th Avenue SW Calgary Alberta T2R 0C5
CONDITION	• Cohort 1 : First-line locally advanced/metastatic unresectable pancreatic ductal adenocarcinoma (PDAC) • Cohort 2 : First-line mCRC, MSI-H or dMMR • Cohort 3 : Third-line mCRC, independent of MSI/dMMR status • Cohort 4 : Second-line (or higher) locally advanced/metastatic unresectable squamous cell carcinoma of the anal canal (SCCA) after prior systemic chemotherapy
DESIGN	multiple-indication, open label, non-randomized
OBJECTIVE(S)	Primary objective To evaluate the response to treatment measured by ORR at week 16 in patients treated with the combination of pelareorep plus atezolizumab as stand-alone therapy (Cohorts 2, 4) or in combination with SOC chemotherapy (Cohorts 1, 3) Secondary objectives To assess the anti-tumor activity of the treatment combinations based on Progression-free survival (PFS) and Overall survival (OS) To evaluate the tolerability of the combination of pelareorep plus atezolizumab as stand-alone therapy (Cohorts 2, 4) or in combination with SOC chemotherapy (Cohorts 1, 3)
INTERVENTION(S)	Cohort 1: pelareorep and atezolizumab added to SOC gemcitabine and nab paclitaxel Cohort 2: pelareorep and atezolizumab Cohort 3: pelareorep and atezolizumab added to SOC trifluridine/tipiracil Cohort 4: pelareorep and atezolizumab
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	To evaluate the immunological changes within tumor tissue and peripheral blood and to examine potential biomarkers of response to treatment in each cohort
BACKROUND/RATIONALE	Within the last 10 years, our understanding of the relationship between the immune system and cancer has led to profound advancements in oncology. Immunotherapy with monoclonal antibodies directed against programmed cell-death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) has changed the treatment paradigm for many cancers. Despite advances in immunotherapy, this therapeutic approach for GI cancers has demonstrated limited efficacy. The checkpoint blockade inhibitors, nivolumab and pembrolizumab, are used for the treatment of only a small subset of pretreated patients with tumors characterized as having a high predisposition for genetic mutations, known as MSI. MSI-H tumors are also immunologically 'hot' and poised to respond to checkpoint blockade therapy through their high number of tumor-infiltrating lymphocytes (TILs), specifically CD8+ T cells, and high levels of PD-L1 expression. Within CRC, MSI makes up approximately 15% of all CRCs and its prevalence is stage-dependent, with ~15% of stage II-III disease and only 4–5% for mCRC (Kalyan et al., 2018). Across all cancers, MSI is present in 3.8% (Bonneville et al., 2017). In contrast, checkpoint blockade has shown little efficacy in tumors with a low number of

	genetic mutations, known as microsatellite stable (MSS) tumors. These MSS tumors are considered 'cold' tumors, having low levels of immune cell infiltration and PD-L1 expression, and comprise most GI cancers. Use of oncolytic virus to sensitize GI tumors to checkpoint blockade. To overcome resistance to immunotherapy within GI cancer, one promising strategy is to increase the number of cytotoxic immune cells within the TME via the use of an oncolytic virus. Oncolytic viruses have shown notable activity in several cancer types and activate both innate and adaptive anti-viral immunological responses that in turn coax anti-tumor immunity (Gujar et al., 2018). In this study, we will explore if the oncolytic virus, pelareorep, can turn 'cold' tumors 'hot' and sensitize GI tumors to checkpoint blockade, thereby improving responses and broadening the number of patients that can be treated. Several existing oncolytic viruses require tumor site injection. This is perceived as a barrier to treatment due to difficulties with accessing these tumors. The oncolytic virus pelareorep is administered intravenously (IV) and is not associated with human disease (Sabin, 1959). Pelareorep is a propriety formulation of a naturally occurring, non-genetically modified, non-enveloped human reovirus serotype 3-Dearing strain, which contains a live, replication-competent virus. Pelareorep selectively kills tumor cells and promotes tumor-directed innate and adaptive immune responses, resulting in the priming of the TME for checkpoint blockade, allowing for treatment with anti-PD-L1 or anti-PD-1 therapies (Samson et al., 2018). Pelareorep has demonstrated in vitro and in vivo activity in many cancers, including CRC and pancreatic cancer, and has been delivered intratumorally (ITu) and IV in clinical studies. Pelareorep's anti-tumor activity is based on a complementary, dual mechanism of action: 1. Direct oncolytic activity in tumor cells permissive to viral replication (Strong et al., 1998; Norman et al., 2002; Kim et al., 2010; Carew et al., 2013). 2. Induction of anti-tumor immunity through: • Innate immunity against virally infected tumor cells and upregulation of inflammatory cytokines (Errington et al., 2008; Prestwich et al., 2009; Steele et al., 2011; Adair et al., 2013; El-Sherbiny et al., 2015). • Adaptive immunity through the increased presentation of tumor- and virus-associated epitopes by tumor cells or antigen-presenting cells, allowing for the generation of an adaptive anti-tumor immune response (White et al., 2008; Prestwich et al., 2009; Gujar et al., 2010; Kim et al., 2015; Rajani et al., 2016). Thus, in addition to functioning as an oncolytic agent, pelareorep overrides the absence of anti-tumor immunity present in cancer patients, activating innate and adaptive anti-tumor immune responses.
KEY EXCLUSION CRITERIA	1. Undergone systemic chemotherapy, radiotherapy, or surgery, <4 weeks before study treatment. 2. Received previous treatment with immune checkpoint inhibitors. 3. Uncontrolled hypertension (systolic blood pressure ≥150 mmHg and diastolic blood pressure ≥90 mmHg) despite treatment with hypotensive agents. 4. Acute coronary syndrome (including myocardial infarction and unstable angina) and/or a history of coronary angioplasty or stent placement performed within 6 months of enrollment. 5. A large amount of pleural effusion or ascites requiring more than weekly drainage. 6. A history of (non-infectious) pneumonitis that required steroids or currently active pneumonitis. 7. A ≥grade 3 active infection according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

	8. Symptomatic brain metastasis. (Patients with asymptomatic and stable brain metastasis are eligible for study enrollment). 9. Interstitial lung disease with symptoms or signs of activity. 10. In C1, C2, and C3 only: Positive test results for either anti human immunodeficiency virus (HIV)-1 antibodies, anti-HIV-2 antibodies, anti-human T cell leukemia virus type 1 (HTLV-1) antibodies, hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV) antibodies.* Testing is not required unless deemed necessary by the investigator. *Patients who test positive for anti-HBc antibodies or have detectable HBV-DNA will also be excluded. In C4 only: Positive test results for either anti HIV-1 or HIV-2 antibodies if the CD4+ T cell is <300 cells/µl.* Testing for HIV status is required. * To be eligible, HIV+ patients must have an undetectable viral load and be receiving highly active antiretroviral therapy (HAART). Patients must be on established HAART therapy for at least 4 weeks prior to study entry. 11. Autoimmune disease that has required systemic treatment in the past 2 years with disease modifying agents, corticosteroids, or immunosuppressive drugs. [Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment]. 12. A history or findings of ≥grade 3 congestive heart failure according to the New York Heart Association functional classification. 13. A seizure disorder that requires pharmacotherapy. 14. Proteinuria ≥grade 3 (using spot testing; if grade 3, repeat with mid-stream urine; if still grade 3, then urine collection for 24 hours to confirm grade) as per NCI CTCAE. 15. A medical contraindication to undergoing biopsies 16. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation. 17. A non-healing wound, non-healing ulcer, or non-healing bone fracture within 4 weeks prior to the start of study drug. 18. Women who are pregnant or breastfeeding. 19. A diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing >10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study drug. 20. Any vaccine during screening and the first cycle of treatment. 21. Legal incapacity or limited legal capacity to consent.
KEY INCLUSION CRITERIA	C1: Locally Advanced/Metastatic Unresectable Pancreatic Ductal Adenocarcinoma 1L • Patients with histologically or cytologically confirmed, locally advanced/metastatic unresectable PDAC who are eligible for 1L SOC chemotherapy with gemcitabine plus nab-paclitaxel C2: Metastatic Colorectal Cancer 1L (MSI-H/dMMR) • Patients with histologically or cytologically confirmed mCRC with MSI-H/dMMR tumors and no prior systemic treatment for metastatic disease C3: Metastatic Colorectal Cancer 3L • Patients with histologically or cytologically confirmed mCRC, independent of MSI/dMMR status, who failed (and/or did not tolerate) 2 prior lines of treatment, including oxaliplatin, irinotecan, 5-FU, ± targeted agents such as bevacizumab and/or an anti-epidermal growth factor receptor (EGFR) antibody who are eligible for 3L SOC chemotherapy with trifluridine/tipiracil C4: Locally Advanced/Metastatic Unresectable Anal Cancer ≥2L

	• Patients with histologically or cytologically confirmed locally advanced/metastatic unresectable SCCA of viral (HPV) or non-viral origin who failed (and/or did not tolerate) prior systemic chemotherapy All Cohorts: Patients must: 1. Provide written informed consent prior to study participation. 2. Be at least 18 years of age on the day of providing consent. 3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days of start of treatment. 4. Have evaluable or measurable lesions per RECIST v1.1. 5. Have adequate organ function at the time of enrollment as defined by: • Absolute neutrophil count ≥1200/mm3 • Platelet count ≥7.5 × 104/mm3 • Hemoglobin >8 g/dL (blood transfusion >2 weeks before testing is permitted) • Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤2.5 x the upper limit of normal (ULN; ≤5 x ULN in patients with liver metastasis) • Total bilirubin ≤1.5 x ULN • Creatinine ≤1.5 x ULN • Lipase ≤1.5 x ULN • International normalized ratio (INR) ≤1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤1.5 x ULN unless receiving treatment with therapeutic anticoagulation. Patients being treated with anticoagulant, e.g. heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring per local SOC will be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local SOC. 6. Have recovered to ≤grade 1 or baseline for all adverse events (AEs) due to previous therapies or surgeries. 7. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly-effective form(s) of contraception (i.e., one that results in a low failure rate [<1% per year] when used consistently and correctly) and to continue its use for 6 months after the last dose of study drug.
STATISTICAL ANALYSIS	All the methods described below will be performed separately in each of the 4 study cohorts. The primary endpoint is calculated by dividing the number of patients achieving CR or PR as best response at week 16 according to RECIST v1.1 by the total number of patients in the ITT population. Exact 90% and 95% confidence intervals will be provided for this proportion. As a sensitivity analysis, a similar calculation will be performed in the per-protocol population. All other efficacy and toxicity parameters will be evaluated in an explorative or descriptive manner, providing proportions, means, medians, ranges, standard deviations and/or confidence intervals, or Kaplan-Meier estimates, as appropriate.
SAMPLE SIZE	A total of 55 patients in all 4 cohorts for the primary endpoint ORR (C1=12; C2=19; C3=14; C4=10), with the option for extension if the predefined clinical efficacy criteria are met
TRIAL DURATION	Total trial duration is expected to be 43 to 50 months. This reflects the expected enrollment period (7 to 14 months) plus the per patient follow-up period (36 months). If any of the 4 cohorts meets the criteria for expansion, the duration of the study will increase accordingly.
PARTICIPATING CENTERS	25 sites planned

FURTHER CENTERS DESIRED?	Yes, site selection is pending