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A Phase 2 study of pembrolizumab in combination with pelareorep in patients with advanced pancreatic adenocarcinoma

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LIST OF ABBREVIATIONS

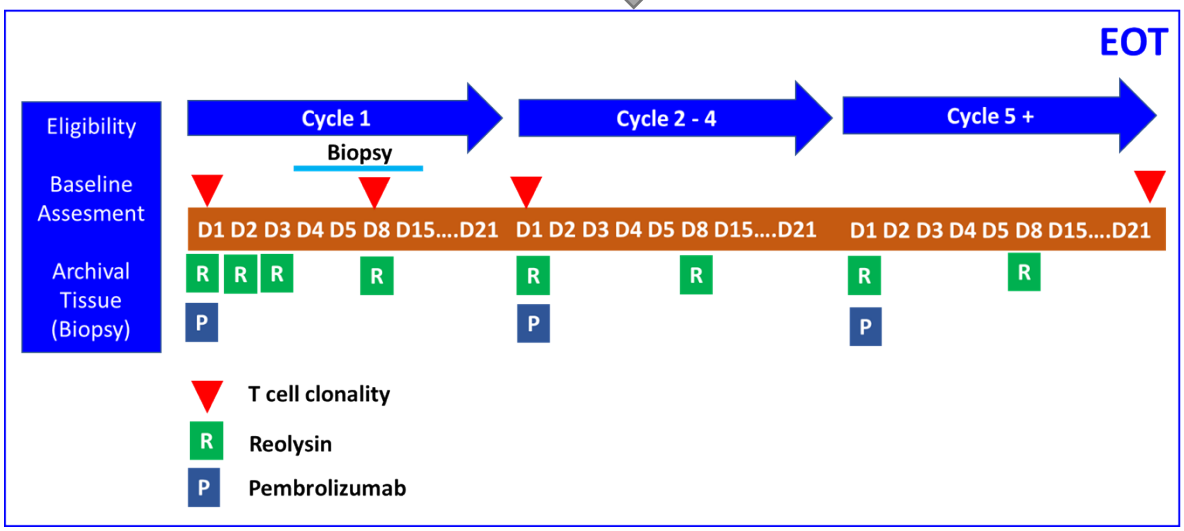
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
APAP	Acetaminophen or paracetamol
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
AUC	Area under the curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CEA	Carcinoembryonic antigen
CI	Combination indices
CIVI	Continuous IV Infusion
CK-MB	Creatinine Kinase MB
CPE	Cytopathic Effects
CR	Complete Response
CRF	Case Report Form
CSF	Colony Stimulating Factor
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Edetic Acid (ethylenediaminetetraacetic acid)
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
FOLFIRI	Irinotecan/Fluorouracil/Leucovorin
5-FU	Fluorouracil
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl-transferase
GM-CSF	Granulocyte-Macrophage-Colony Stimulating Factor
Hb	Hemoglobin
HCl	Hydrochloride
HIV	Human Immunodeficiency Virus
HSV-1	Herpes simplex virus 1
IRB	Investigational Review Board
ITu	Intratumoral Injection
IV	Intravenous
IL	Interleukin
INF	Interferon
L	Litres
LD	Longest Diameter

LDH	Lactic dehydrogenase
LHRH	Luteinizing Hormone-Releasing Hormone Analog
LV	Leucovorin
MDSCs	Myeloid derived stem cells
mg	Milligram(s)
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease
PD-1	Programmed death 1
PDGFR	Platelet Derived Growth Factor Receptor
PD-L1 and 2	Programmed death ligand 1 and 2
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PFU	Plaque forming units
PKR	Double-stranded RNA- activated Protein Kinase
PR	Partial Response
PT/PTT	Prothrombin Time/Partial Thromboplastin Time
RECIST	Response Evaluation Criteria In Solid Tumors
iRECIST	Immune- Response Evaluation Criteria In Solid Tumors
REO	Respiratory Enteric Orphan
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SCID	Severe Combined Immune Deficient
SCID-NOD	Severe Combined Immune Deficient Non-Obese Diabetic
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SI	International System of Units
$TCID_{50}$	Tissue Culture Infective Dose $_{50}$
Th1/2	T helper phenotype 1 and 2
TNF	Tumor necrosis factor
Tmax	Time to maximum observed plasma concentration after dose
ULN	Upper Limit of Normal
US	Ultrasound
VSV	Vesicular Stomatitis Virus
WBC	White Blood Cells

STUDY SCHEMA

Phase II combination study
Pelareorep + Pembrolizumab

Simon 2-stage optimum design (total 30 patients)
Stage I: sample size 11 evaluable patients. If >=2 meet pre-specified criteria, proceed to Stage II: At least 7 of 30 responses required to reject null hypothesis.



1 cycle =21 days (+/-3 days)

Primary objective: ORR of the combination by RECIST v 1.1 criteria.

Tumor assessment by CT or MRI at baseline and the last week of Cycles 3, 6, 9 etc. (Every 3 cycles). For patients that discontinued due to toxicity, tumor evaluations should be performed until PD is noted.

Follow-up for survival outcome: every 3 months by a telephone call or clinic visit at the discretion of the investigator.
Note: Follow-up will be for a maximum of 2 years.

STUDY SUMMARY

Title	A Phase 2 study of pembrolizumab in combination with pelareorep in patients with advanced pancreatic adenocarcinoma
Version	3.23.2020 Amendment 2
Study Design	Phase II, single arm open label, Simon two-stage optimum design
Study Center(s)	Robert H. Lurie Comprehensive Cancer Center, Northwestern University
Objectives	Primary Objectives: • To determine the overall response rate (ORR) by RECIST v 1.1 criteria of pembrolizumab in combination with pelareorep. Secondary Objectives: 1. To determine progression free survival by RECIST v 1.1 criteria, as well as 1-year, 2-year and median overall survival of pembrolizumab in combination with pelareorep. 2.To determine safety and tolerability of pembrolizumab and pelareorep when administered in combination as determined by NCI CTCAE v 4.03. 3. To determine the effects (immune response) of pembrolizumab and pelareorep when administered in combination as determined by analysis of pre-and post-treatment biopsies and blood-based immune markers.
Sample Size	Up to 30 patients (11 patients will be enrolled in Stage 1 and up to 19 additional patients will be enrolled in Stage 2, if pre-specified criteria for Stage 2 are met in Ph2-S1. The pre-defined criteria states that, for the primary objective >=2 or more responses out of 11 are required in Stage 1 to continue the trial to the full 30 patients). Total enrollment: 13 patients in Stage I/ 21 patients in Stage 2 Evaluable patients: 11 patients in Stage I/19 patients in Stage 2
Diagnosis & Key Eligibility Criteria	Inclusion Criteria: • Patients must have histologically confirmed advanced (unresectable or metastatic) pancreatic adenocarcinoma, documented objective radiographic progression and have failed or not tolerated first-line therapy. • Patients must have an ECOG Performance Score ≤ 1. • Patients must have a life expectancy of ≥ 6 months. Exclusion Criteria: • Patients who have had chemotherapy or radiotherapy within 4 weeks prior to day 1 of study drug and those who have not recovered from adverse events due to agents administered more than 4 weeks before C1D1 are not eligible. • Patients with a known active central nervous system (CNS) metastases and/or carcinomatous meningitis are excluded. See Section 3 for the full list of Eligibility Criteria.

<table>
<tr><td>Treatment Plan</td><td>Pembrolizumab will be administered on Day 1 at 200 mg IV over 30 minutes.

Pelareorep on Day 1 will be administered after completion of Pembrolizumab infusion.

In Cycle 1, Pelareorep will be administered at a dose of $4.5x10^{10}TCID_{50}$ on Days 1, 2, 3 and 8. From Cycle 2 onwards, Pelareorep will be administered at a dose of $4.5x10^{10}TCID_{50}$ on Days 1 and 8.
Each cycle is 21 days (3 weeks). Up to 32 cycles of pembrolizumab and 24 months of Pelareorep (2 years) of therapy can be administered.

Medication schedule and dose
<table>
<tr><td>Dose Level</td><td>Pelareorep $4.5x10^{10}$ $TCID_{50}$</td><td>Pembrolizumab 200 mg</td></tr>
<tr><td>Cycle 1</td><td>Days 1,2,3,8</td><td>Day 1</td></tr>
<tr><td>Cycle 2 +</td><td>Days 1, 8</td><td>Day 1</td></tr>
</table>
</td></tr>
<tr><td>Statistical Methodology</td><td>This Phase 2 study follows a Simon’s two-stage optimum design to evaluate the efficacy of pembrolizumab in combination with Pelareorep. The “Go/No Go” criteria in Phase 2 (Stage 1) will be defined using null response rate, alternative response rate, power, and alpha. In Stage 1, with null rate 10%, alternative rate 35%, power 90%, and 1-sided alpha 0.025, the Simon two-stage "optimum" design specifies stage 1 sample size of 11, stopping for futility if <= 1 response out of 11 in stage 1, and adding 19 additional patients if >= 2 responses at stage 1. In Stage 2, at least 7 responses out of 30 are required to reject null rate of <10%.</td></tr>
</table>

1. INTRODUCTION - BACKGROUND AND RATIONALE

A comprehensive summary is included in the Investigator's Brochures. A brief overview is included below with emphasis on combination studies.

1.1 Disease Background

Pancreatic adenocarcinoma (AC) remains one of the most lethal of human malignancies. It is the fourth leading cause of cancer-related death in the United States. The majority of patients are diagnosed with advanced stage disease, and as such, for the large majority of patients, will succumb to their disease. Despite significant advances in improvements in cancer therapy, mortality for pancreatic cancer has remained relatively unchanged. The mainstay of treatment for patients with advanced pancreatic adenocarcinoma remains systemic combination chemotherapy. The most common combination used in first line setting is FOLFIRINOX or gemcitabine plus nab-paclitaxel (Abraxane) chemotherapy. Despite this, patient outcomes remain poor, with 5-year survival of less than 10%. Development of new therapies for pancreatic AC is greatly needed.

1.2 Interventional Background & Overview

1.2.1 Oncolytic Virotherapy

Oncolytic viruses are viral strains capable of selective killing of malignant cells while leaving normal cells essentially unaffected [4]. Some viruses, like Reovirus, have a natural tropism for malignant cells while others, like adenovirus or measles, have to be genetically engineered in order to recognize specific cancer cell receptors [5]. Oncolytic viruses were first used in the 1950s as an experimental cancer treatment, but modern oncolytic virotherapy began in the 1990s after it was shown that an attenuated HSV strain is active in a murine glioblastoma model. Since then, oncolytic viruses belonging up to 10 different families have been tested in clinical trials [5]. Oncolytic viruses represent a new class of therapeutic agents that promote anti-tumor responses through multiple mechanisms of action that are dependent on selective tumor cell killing and the induction of systemic anti-tumor immunity. The molecular and cellular mechanisms of action likely depend on viral replication within transformed cells, induction of primary cell death, interaction with tumor cell antiviral elements and initiation of innate and adaptive anti-tumor immunity [5]. A unique aspect of oncolytic viral treatments is that self-replicating viral factories are established within the tumor cells with a potential for continued effect after treatment.

1.2.2 Reovirus

Reovirus Serotype 3 – Dearing Strain is a naturally occurring, ubiquitous, non-enveloped human Reovirus with a genome that consists of 10 segments of double-stranded RNA [6].

The *Reoviridae* family of viruses consists of six genera, three of which infect animals (including humans) and three which infect only plants and/or insects [6]. Of the three which can infect humans – Reovirus, orbivirus, and rotavirus – the Reovirus appears to cause the least pathology. Reoviruses are found throughout the world and their pathology appears to result in only minor respiratory or enteric symptoms in humans, and to be nonexistent in other animals. The term Reovirus stands for Respiratory Enteric Orphan virus; an orphan virus being one that is not associated with a known disease state [7].

The Reovirus is a non-enveloped virus, with a double-shelled capsid, each with icosahedral symmetry, and containing 10 linear double-stranded RNA genome segments [6]. There are three distinct serotypes based upon neutralization and hemagglutination inhibition tests [8]. The prevalence of Reovirus antibodies in adult humans has been found to be >50% up to 100%, depending on the study [9-12].

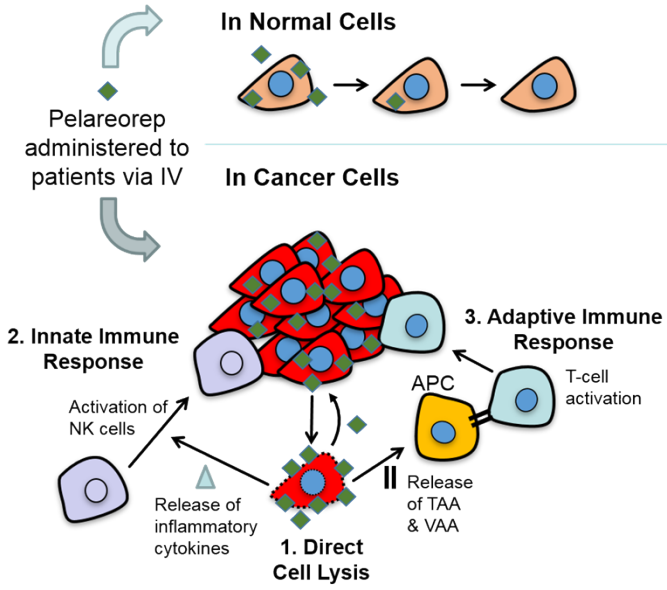
During naturally occurring Reovirus infections in immunocompetent animals, the pathogenic effects appear to be minimal. The infectious cycle begins when the viral particles are converted in the GI tract to intermediate subviral particles (ISVPs) due to the action of proteolytic enzymes [13]. Reoviruses initially infect the epithelial cells of the ileum [14, 15], and are thought to then cross through the intestinal M cells, moving to the Peyer's patches, then to the mesenteric lymph nodes through lymphatic dissemination. Eventually Reoviruses move through the blood stream to extraintestinal organs and the central nervous system [16]. Although it can infect many different organs, the Reovirus produces very minor, or no, illness.

1.2.3 Pelareorep Mechanism of Action

Pelareorep is the **first-in-class immuno oncology- viral agent** for **systemic administration** that induces lysis of cancer cells and innate and adaptive immune responses that lead to an **inflamed tumor phenotype** and **anti-tumor activity**. Pelareorep (also known as REOLYSIN) contains a type 3 Dearing Reovirus, which is a naturally occurring virus that is **not** genetically modified.

Pelareorep's activity is based on three modes of action, which are complementary but not interdependent:

- Selective viral replication in permissive cancer cells which leads to tumor lysis [17, 18]
- Activation of innate immunity in response to the infection which results in a cascade of chemokines/cytokines causing natural killer (NK) cells to recognize and attack cancer cells [19]
- A specific adaptive immune response triggered by tumor- and viral-associated antigens displayed by antigen-presenting cells (APCs, infected tumor cells and/or dendritic cells) to T cells [20-22]



In non-cancer cells pelareorep enters the cells but is unable to replicate and the virus is actively cleared.

1. Pelareorep selectively replicates in permissive cancer cells. Upon virus replication, cancer cells lyse/die releasing additional virus particles (◆) to infect nearby cancer cells.

2. Pelareorep replication causes the release of inflammatory cytokines (△) which activate Natural Killer (NK) cells, allowing NK cells to attack cancer cells.

3. Antigen presenting cells (APCs) display tumor- and viral-associated antigens (TAA/VAA, ‖) to killer T-cells, activating an adaptive anti-cancer immune response.

Reovirus replication is entirely cytoplasmic and replication does not include any intranuclear events [21]. Treatment with PELAREOREP does not constitute gene transfer or gene therapy.

1.3 Pre-Clinical Experience

In the NCI 60-cell screen, the majority of cell lines derived from NSCLC, colon, and ovarian cancers were permissive to Reovirus-induced cytopathic effect (CPE). Breast cancer and leukemia cell lines showed varying degrees of susceptibility to Reovirus-induced CPE (Shizuko Sei, personal communication).

1.3.1 Combination of Pelareorep with Chemotherapy

Studies of Pelareorep in combination with chemotherapeutic agents (like gemcitabine, paclitaxel/carboplatin) in human cancer lines, animal models [23-25] and in humans [26-30] have shown synergy and/or additive effects. For example, cells from the human colorectal cancer cell line HCT-116 were exposed to either Reovirus alone, a cytotoxic agent alone (gemcitabine, fluorouracil, cisplatin and doxorubicin), or escalating virus and drug combinations. Median effects analysis revealed that Reovirus was synergistic with the drug across a wide range of drug concentrations [24]. Additional cytotoxic drugs including mitomycin and taxanes exhibit this effect [23]. Furthermore, *in vivo* studies using subcutaneous implants of RAS transformed fibroblasts (C3H-10T1/2) in immunocompetent C3H mice suggest that Reovirus may be useful to overcome resistance to cisplatin and possibly other chemotherapies (Oncolytics, data on file).

1.3.2 Studies of Reovirus as an Infective Agent

Studies in which volunteers were inoculated with the three serotypes of Reovirus resulted in symptoms of illness in only approximately one-third of the volunteers [8]. These symptoms included malaise, rhinorrhea, cough, sneezing, pharyngitis, headache, and loose stool. There have been isolated reports implicating Reovirus with other disease processes such as hepatobiliary, neurological, respiratory, or exanthematous disease, although these reports are incomplete and may reflect only chance associations, or the extent of the virus in the environment. In order to ascertain the clinical features of Reovirus infection, one study was undertaken in 1963 in which each of the three serotypes of Reovirus was inoculated into adult volunteers [8]. In this study, 27 male volunteers from various minimal security correctional institutions were given intranasal inoculations of one of the three serotypes of Reovirus and followed for 23 days for signs of symptomatic illness. Of the nine men receiving Reovirus type 1, only three showed signs or symptoms of illness, which included malaise, rhinorrhea, cough, sneezing, pharyngitis and headache. These signs and symptoms typically had an onset within 24 to 48 hours and lasted from 4 to 7 days. There was also one report of “loose stools” in another volunteer. Reovirus type 2 inoculations were associated with similar signs, symptoms and durations in three of the nine volunteers with such exposure. Two of the nine volunteers receiving Reovirus type 3 inoculations developed mild rhinitis. None of the volunteers showed any other physical signs or symptoms, or any significant laboratory abnormality (including routine blood counts, urinalysis, chest X-ray, liver function studies, electrocardiogram, and bacteriologic examinations of nose, throat, and faeces). None of these patients developed a fever. This confirmed that Reovirus may cause minor upper respiratory tract illnesses, as had been previously suggested and confirmed subsequently [11, 31-33]. Other studies have shown Reovirus to be excreted in urine and stool.

1.3.3 Clinical Trials of Pelareorep

Pelareorep was administered intravenously every 4 weeks in a cohort of 18 patients with advanced heavily pretreated solid malignancies in the phase I REO 004 trial [34]. Doses up to 3×10^{10} $TCID_{50}$ were administered with no grade >3 adverse effects. The most common adverse effects were fevers, myalgia and nausea and they were grade 1. The best response was partial response in one patient with breast cancer harboring a RAS codon 12 mutation [glycine (GGT) to alanine (GCT)] in her tumor. Seven more patients had stable disease.

In another phase I trial (REO 005), Pelareorep was administered to 33 patients in doses up to 3 x 10^{10} $TCID_{50}$ on a schedule of up to 5 consecutive doses every 4 weeks [35]. No dose-limiting toxicities were experienced. The most common toxicity was grade 1-2 flu like illness, 2-6 hours after the infusion that responded to antipyretics and NSAIDs. The most common grade >3 toxicity was flu-like illness (grade 3) and uncomplicated lymphopenia and neutropenia. Best response was stable disease, with some patients experiencing minor decreases in the sum of the maximum diameters of the target lesions.

1.3.4 **Clinical trials of Pelareorep in combination with chemotherapy and radiation**

As discussed above, co-administration of cytotoxic agents may enhance the antitumor effect of reovirus. Radiation therapy may also enhance its antitumor effect. Herein we present 4 studies of relevance to the current protocol.

In a phase I study in 24 patients with advanced malignancies eligible for treatment with docetaxel, reovirus was co-administered with docetaxel [36]. Docetaxel was given at a dose of 75 mg/m^2 every 21 days (with standard steroid premedication). Pelareorep was administered in doses up to 3 x 10^{10} $TCID_{50}$ 5 days a week every 21 days. The toxicities were as expected for docetaxel and Pelareorep based on previous experience. Flu-like symptoms was the most common side effect attributable to the study drug with only one grade 4 event (in cohort 1, 3 x 10^9 $TCID_{50}$). They typically occurred 2 to 4 days after reovirus administration and were easily controlled with acetaminophen and nonsteroidal anti-inflammatory medication. Symptoms seemed to be more common in the first cycle of treatment and milder in subsequent cycles. Only one patient exhibited systemic viral shedding by PCR. One patient had a complete response (breast cancer) and 3 more attained a partial response. Three patients had stable disease. Neutralizing antibody formation was increased in all patients. In all available post treatment biopsy specimens, there was cytoplasmic evidence of viral protein expression.

In a phase I dose escalation study in patients with advanced malignancies, Pelareorep was administered in combination with gemcitabine [26, 28]. The side effect profile was compatible with previous experience with both Pelareorep and gemcitabine. Of the 10 patients available for response assessment, one patient with nasopharyngeal carcinoma attained a partial response by RECIST criteria, while a heavily pretreated patient with breast cancer attained a significant clinical improvement in her symptoms with minor radiological response. Compared to phase I studies of Pelareorep as monotherapy, the combination with gemcitabine led to attenuation in the neutralizing antibody production.

The combination of Pelareorep with the combination of irinotecan/5-FU/leucovorin (FOLFIRI) was studied in a phase I study in patients with RAS mutated metastatic colorectal cancer [37]. Patients who had received FOLFIRI in the past were eligible and consisted of more than half of the study population (13/21). The combination was safe, well tolerated and no new toxicities were identified. The dose-limiting toxicity (DLT) was neutropenia. Of the 18 patients evaluable for response, 5% attained a partial response and 50% had stable disease. Median progression free survival (PFS) for the FOLFIRI-naïve patients was 7.4 months while for the FOLFIRI non-naïve patients was not reached.

In another phase I study, 18 patients with advanced solid tumors with measurable disease amenable to treatment with localized short-course palliative radiation treatment, were treated with radiation in combination with ITu administration of reovirus [30]. There was no exacerbation of acute toxicities from radiation. Again,

the side effect profile of reovirus was expected and easily manageable and there was no systemic viral shedding. Three patients had significant partial responses.

1.3.4.1 **Pelareorep in pancreatic cancer**

Preclinical data indicate activity for reovirus in pancreatic cancer [38, 39] A Phase I, open-label, dose escalation study of the combination of reovirus and gemcitabine that aimed to determine the safety and tolerability of systemic reovirus when administered with gemcitabine treatment was conducted [28]. Sixteen patients were treated. MTD was not formally established but $1x10^{10}$ $TCID_{50}$ of reovirus on Day 1and gemcitabine 1,000 mg/m^2 Day 1 and Day 8 of a 21-day cycle was the preliminary recommended Phase II dose. The combination of reovirus and gemcitabine did not alter gemcitabine pharmacokinetics and if reovirus was given on Day 1 of each cycle, toxicity was predictable except for elevations in ALT. However, these liver enzyme changes are mild, transient and the clinical relevance of these changes is unclear. The combination of reovirus and gemcitabine shows some clinical activity in this highly pretreated patient population.

The Oncolytics' sponsored REO 017, a single arm Phase II study was conducted in the USA (Cancer Therapy & Research Center - CTRC, San Antonio, Texas and Montefiore Cancer Center, Bronx, NY) and evaluated Pelareorep in combination with gemcitabine in chemotherapy-naïve patients with advanced pancreatic adenocarcinoma. The primary endpoint was the clinical benefit rate in terms of Complete Response (CR) + Partial Response (PR) + Stable Disease (SD) at 12 weeks in >8 patients out of 33 as the alternative hypothesis. The secondary endpoints included PFS and OS. Gemcitabine was administered IV at a dose of 800 mg/m^2 on Days 1 and 8 every 21 days, while pelareorep was administered IV over 60 minutes at $1x10^{10}$ $TCID_{50}$ on Days 1, 2, 8 and 9 every 21 days. The planned 34 patients had been enrolled in the study as of September 2012 and data reported by Mahalingam *et al*. [40] in 2015. The treatment was well tolerated with non-hematological toxicities including asthenia fever, chills, flu-like syndrome, nausea, and vomiting. Two patients had grade 3 neutropenia. At a survival update in February 2015 including all recruited 34 patients (29 evaluable patients for response) one patient had a PR, 23 patients had SD, five patients had PD as the best response; overall, 18 patients had a clinical benefit measured as PR/SD ≥12 weeks thus meeting the alternative hypothesis. The survival analysis based on 33 evaluable patients shows a median PFS of 4 months; median OS was 10.2 months with 1-year and 2-year survival of 45% and 24% respectively.

Another study was recently completed by NCI and recently reported [41]. The primary objective of the study was to assess the improvement in PFS with pelareorep in combination with carboplatin/paclitaxel relative to carboplatin/paclitaxel alone in patients with recurrent or metastatic pancreatic cancer. Patients with disease progression could crossover to the Pelareorep arm. The study enrolled 73 patients; 37 were in the control arm, 36 were in the test arm. The median PFS for the control arm was 5.2 months versus 4.9 months for the test arm Given that the control arm outperformed the pre-study assumptions for efficacy (over 5 months vs expected 3 months) the net result is to be considered in light of the study consequently becoming underpowered for the primary endpoint. Despite the negative results when comparing the PFS, an Ad-Hoc analysis of the survival data (conducted by Oncolytics) showed a possible delayed effect on OS, with a divergence of survival curves occurring around year 1, and the strongest efficacy signal for improvement in OS occurring around year 2. The comparison of survival

probability at year 2 found a potentially promising efficacy signal. The probability of survival at year 2 was 20% in the test arm vs 9% in the control arm. This difference yields a Z-score of Z=1.27 and two-sided p-value of 0.20 using the log-log method (Klein et al. 2007). Most common grade 3-4 toxicities included neutropenia (53%) and leucopenia (36%) with no overall difference between arms. Furthermore, the addition of REOLYSIN to carboplatin + paclitaxel was well tolerated and induced CD4+/CD8+ T-cell activation.

1.3.5 Summary of Clinical Safety Data

A total of 1417 patients have been enrolled in clinical studies conducted in the US, Canada and EU. Of these, 1027 patients have received pelareorep, 936 via intravenous (IV) administration and 91 by intratumoral injections (ITu). The remaining 390 patients were randomized to control arms.

Pelareorep has been administered as single or multiple doses IT IV, either as a mono-therapy or in combination with chemotherapy, immunotherapy (e.g., checkpoint point inhibitors), and radiotherapy.

No Maximum Tolerated Dose (MTD) for intravenous Pelareorep as mono-therapy was defined in the two Phase 1 trials (REO 004 and 005) [34, 35]. When combined with chemotherapeutic agents, Pelareorep does not appear to enhance either the frequency or severity of the adverse effects of the chemotherapeutic agents. However, most patients may experience a transient, mild to moderate “flu-like syndrome” after IV administration, including fever, chills, headache, fatigue, rhinorrhea, cough, myalgia and/or arthralgia, as well as GI symptoms, including nausea, vomiting, and diarrhea. Moderate and transient alterations in hepatic function tests and hematology values have also been observed. See the Investigator’s Brochure for additional information.

1.4 Immune Checkpoint Inhibition in Cancer Treatment

PD-1 (programmed death-1) is an important regulator of the lymphocyte activation/de-activation process. Upon binding to its ligand, PD-L1, can lead to cell energy and death [42]. PD-1 expression is up-regulated on tumor infiltrating lymphocytes and PD-L1 expression has been shown on a wide variety of solid tumors [42]. PD-L1 expression can be part of the innate tumor behavior (innate immune resistance) or it can be induced as part of the tumor adaptation to selective pressure from the immune system (adaptive immune resistance) [43].

Nivolumab and pembrolizumab are IgG4 (fully human and humanized respectively) antibodies targeting PD-1. These agents are approved by the Food and Drug Administration (FDA) for treatment of advanced melanoma and squamous non-small cell lung cancer (NSCLC) [2, 44]. Increased PD-L1 expression is associated with an improved response rate in patients with melanoma and NSCLC treated with pembrolizumab [45, 46]. On the contrary there was no difference based on the PD-L1 status in patients with squamous NSCLC treated with nivolumab [47]. Data from patients with advanced melanoma treated with ipilimumab, a monoclonal antibody against CTLA4-the prototype checkpoint inhibitor, show that the patients deriving most benefit from immunotherapy are those who have tumors harboring highly immunogenic neo-epitopes in the cell surface [48].

1.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-

cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.4.2 Rationale for Dose Selection/Regimen/Modification of pembrolizumab

The clinical development of pembrolizumab, was initiated through an open-label Phase I trial (Protocol 001) to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels

(1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

1.5 Pelareorep and Checkpoint Inhibitors

Oncoviruses can augment the antineoplastic activity of checkpoint inhibitors as well as increase immunogenicity of poorly immunogenic tumors, as shown with the Newcastle Disease Virus and anti-CTLA4 antibody in melanoma and prostate adenocarcinoma models [49].

Recent studies suggest that pelareorep may enhance the efficacy of antibodies targeting the programmed cell death protein 1 (PD1)/ programmed death ligand 1 (PD-L1) interaction to limit the growth of subcutaneous tumors in preclinical models [50, 51]. The combination of pelareorep and anti-PD-1 therapies augmented anti-tumor T-cell interferon IFN-gamma secretion and NK cell killing of tumor cells in a murine melanoma model [52]. Similarly, in pancreatic adenocarcinoma patients given carboplatin and paclitaxel with or without pelareorep , only patients who received pelareorep had significantly increased expression of the checkpoint molecule CTLA4 (cytotoxic T-lymphocyte-associated protein 4) on both CD4+ and CD8+ T-cells subsets [53]. Upregulation of immune checkpoint marker PD-L1 was also observed in patients with pancreatic adenocarcinoma treated with pelareorep and gemcitabine [54]. Thus, in addition to the role of these checkpoint molecules as biomarkers of anergic or exhausted T-cells, they also represent actionable targets, which may be used to test diverse combination therapies with pelareorep.

Preclinical studies indicate the combination of oncolytic virus therapy with immune checkpoint inhibitors may be more beneficial than either therapy alone. Recently, Liu et al (2015) demonstrated that CD8+ enriched splenocytes co-cultured with pelareorep secreted increased levels of IFN-gamma, therefore suggesting reovirus recognition by CD8+cells and proinflammatory response stimulation via IFN-gamma secretion.[56] Synergistic activity of reovirus with immune checkpoint inhibition has recently been demonstrated in vivo, as the combination of reovirus with PD-1 blockade prolonged survival of mice compared to mice administered either treatment alone. Using an immune-competent mouse model, reovirus was injected intratumorally into subcutaneous B16 melanomas of C57BL/6 mice, and anti-PD-1 was administered intravenously. The combination: induced IFN-gamma secretion in response to B16 tumor-associated antigens; enhanced NK cell-mediated tumor cell death; and attenuated tumor-specific immunosuppression [52]. These results suggest that reovirus oncolytic viro-immunotherapy and immune checkpoint inhibitor therapy can be combined for enhanced therapeutic efficacy.

1.6 Rationale for Current Study

In a Phase 1b study, we hypothesized that reovirus, when combined with low doses of chemotherapy would lead to increased viral replication and oncolysis in RAS activated tumors, with resulting immunogenic response that can be further enhanced by checkpoint inhibition using pembrolizumab. However, even when the treatment was tolerated in the first 11 patients treated in this safety phase of the study, a total of 73% of patients experienced grade 3/ 4 toxicity. There were no discontinuations due to therapy but doses were missed or delayed in four patients. The Pelareorep dose and schedule used was otherwise well tolerated and no PELAREOREP-related excess toxicity was observed in the dose and schedule schema tested. Interestingly, there was one patient with a partial response that lasted 6 months and two patients with stable disease lasting 126 and 221 days.

Furthermore, on-treatment tumor biopsies showed reovirus RNA and immune infiltrates [55]. Thus, for this Phase 2 study we hypothesize that the administration of pembrolizumab in combination with Pelareorep (without chemotherapy) will still have clinical activity in this indication based on the discussion above. Furthermore, by removing chemotherapy, we expect to improve the safety profile and compliance to the therapy that may actually improve the clinical outcomes seen with the triple combination. For this Phase 2 study, we propose to modify the dose scheme of both drugs to optimize their delivery to the tumor site and induce an optimal immune response. On one hand, Pelareorep needs to get to the tumor to promote immune-cell infiltration and the expression of PD-1 and PD-L1 (i.e., inflamed tumor phenotype) so pembrolizumab can exert the maximum benefit. But it is known that the majority of the patients develop neutralizing antibodies in the first 30 days of therapy with Pelareorep [57]. And although Pelareorep can be delivered to the tumor site in the presence of neutralizing antibodies [58.59.60], we propose to increase the viral load administered in the first cycle (Days 1, 2, 3, and 8) and to keep boosting the system with a further two administrations per cycle (Days 1 and 8) thereafter, to give pembrolizumab a better chance to

act. On the other hand, pembrolizumab will be administered as a flat dose of 200 mg every 3 weeks instead of using a ponderal dosing. This will reduce inter-subject variability. Pembrolizumab will be given on Day 1 of each cycle prior to the administration of Pelareorep.

This Phase 2 trial will have a Simon's 2-stage design where responses will be evaluated in Stage 1 according to RECISTv1.1 criteria. If predefined response criteria (for the primary objective, 3 or more responses out of 16 are needed in Stage 1 to continue the trial to the full 30 patients) are met in Stage 1, additional patients will be evaluated in Stage 2. All patients in Phase 2 will also be evaluated by RECIST 1.1 criteria and survival. Also, we expect that clinical responses will be correlated with the presence of an "inflamed phenotype" (as detected by gene-expression profile) and the emergence of selective T & B cell clones against tumor- or viral associated antigens after the start of therapy (T cell clonality in blood).

1.6.1 **Rationale for Pelareorep (REOLYSIN) dose selection for this study**

In studies where REOLYSIN® was combined with chemotherapeutic agents, the MTD for REOLYSIN® has also not been reached). Reolysin® was even administered in doses up to 3 x 10^{10} $TCID_{50}$ 5 days a week every 21 days. The AEs and SAEs were comparable with those reported for the chemotherapy itself. There is no evidence that the addition of REOLYSIN® to any of the chemotherapies led to an increase in the frequency or severity of the AEs generally associated with the chemotherapies themselves.

*(Ref: Comins C, Spicer J, Protheroe A, Roulstone V, Twigger K, White CM, Vile R, Melcher A, Coffey MC, Mettinger KL et al: **REO-10: a phase I study of intravenous reovirus and docetaxel in patients with advanced cancer**. Clinical cancer research : an official journal of the American Association for Cancer Research 2010, **16**(22):5564-5572.)*

2. OBJECTIVES

2.1 Primary Objectives

1. To determine the overall response rate (ORR) by RECIST v 1.1 criteria of pembrolizumab in combination with pelareorep.

2.2 Secondary Objectives

1. To determine progression free survival by RECIST v 1.1 criteria, as well as 1-year, 2-year and median overall survival with pembrolizumab in combination with Pelareorep.

2. To determine safety and tolerability of pembrolizumab and pelareorep when administered in combination as determined by NCI CTCAE v 4.03.

3. To determine the effects (immune response) of pembrolizumab and pelareorep when administered in combination as determined by analysis of pre-and post-treatment biopsies and blood-based immune markers.

2.3 Exploratory Objectives

1. To measure the overall response rate (ORR) by using iRECIST criteria, for the combination of pembrolizumab and Pelareorep

2. To determine progression free survival by iRECIST criteria as well as 1-year, 2-year and median overall survival with pembrolizumab in combination with PELAREOREP

(Please refer to Section 6.0 for details).

3. PATIENT ELIGIBILITY

The target population for this study is patients with advanced or metastatic pancreatic adenocarcinoma. This will be a single-center trial conducted at Northwestern University. A total of 11 patients will be enrolled in Stage 1 and up to 19 additional patients will be enrolled in Stage 2. Approximately 4 potentially eligible patients are seen per month, and it is anticipated that at least 1-2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Devalingam Mahalingam, at (312) 472-1234.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically confirmed advanced (unresectable or metastatic) pancreatic adenocarcinoma, documented objective radiographic progression and have failed or not tolerated first-line therapy.

Note: First-line therapy denotes systemic chemotherapy for advanced pancreatic adenocarcinoma. Only one line of therapy is permitted in this setting.

3.1.2 Patients must have confirmation of an existing formalin-fixed paraffin-embedded (FPPE) tumor sample from archival tissue or from a fresh biopsy of a primary or metastatic lesion at baseline, either as a block or unstained slides for performance of correlative studies.

Note: Patients must undergo a fresh biopsy if archival tissue is not available. Please refer to laboratory manual for more details.

3.1.3 Patients must have measurable disease as defined by RECIST v 1.1.

3.1.4 Any major surgery (except biopsies) must have occurred at least 28 days prior to first day of study treatment.

3.1.5 Be at least 18 years of age.

3.1.6 Patients must have an ECOG Performance Score ≤ 1.

3.1.7 Patients must have a life expectancy of ≥ 6 months.

3.1.8 Patients must demonstrate adequate organ function prior to registration as defined in table below**Error! Reference source not found.**:

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /mcL (with or without growth factor use)
Platelets	≥ 100,000 / mcL
Hemoglobin	≥ 9 g/dL, **OR** ≥ 5.6 mmol/L with (if clinically indicated)/ without transfusion or EPO dependency)
Renal	
Serum creatinine, **OR** Measured or calculated creatinine clearance	≤ 1.5 x upper limit of normal (ULN), **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 x

(GFR can also be used in place of creatinine or CrCl) *(Note: Creatinine clearance should be calculated per institutional standard.)*	institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 x ULN, **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN, **OR** ≤ 5 x ULN for subjects with liver metastases
Albumin	≥ 2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy For patients on anticoagulant therapy, PT/INR must be within therapeutic range
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy For patients on anticoagulant therapy, PT/INR must be within therapeutic range

3.1.9 Patients must meet the following prior to registration:

- TSH, T4 within normal range.
  Note:If a thyroid function test is abnormal, but not deemed clinically significant by treating physician, approval may be given by principal investigator upon discussion.

- Proteinuria within institutional normal or ≤ grade 1 **OR** Urinary protein < 1 g/24hr.

3.1.10 Female subject of childbearing potential must have a negative urine or serum pregnancy within 7 days of registration. It is to be repeated on Day 1 of study treatment, before infusion, if it is done greater than 3 days of Day 1. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.

Female subjects of childbearing potential must be willing to use an adequate method of contraception (willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity), for the course of the study through 120 days after the last dose of study medication (Refer to Appendix 1). *Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.*

Note: A FOCBP is *any woman* (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- *Has not* undergone a hysterectomy or bilateral oophorectomy
- Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months).

3.1.11 Male subjects of childbearing potential must agree to use an adequate method of contraception or be surgically sterile or abstain from heterosexual activity, starting with the first dose of study therapy through 120 days after the last dose of study therapy (Refer to Appendix 1).

3.1.12 Patients must have signed an informed consent indicating that the patient is aware of the neoplastic nature of their disease and have been informed of the procedures of the protocol, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

3.1.13 Patients must be willing and able to comply with scheduled visits, the treatment plan, and laboratory tests.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks prior first day of study drug or those who have not recovered from adverse events due to agents administered more than 4 weeks from Cycle 1 Day 1 are not eligible.

3.2.2 Patients who have a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment are excluded.

Note: If patient is on high dose of steroid therapy, it needs to be brought down to <10mg prednisone or equivalent for at least 7 days prior to Day 1 of study treatment.

3.2.3 Patients receiving any other investigational agents for at least 4 weeks before the first dose of study treatment are not eligible.

3.2.4 Patients with a known history of active TB (Bacillus Tuberculosis) are excluded.

3.2.5 Patients with a hypersensitivity to pembrolizumab or any of its excipients are excluded.

3.2.6 Patients who have had a prior anti-cancer monoclonal antibody (mAb) within 28 days prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

3.2.7 Patients who have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 28 days prior to study Day 1 or who has not recovered (i.e., NCI CTCAE version 4.03[3] Grade ≤1 or at baseline) from adverse events due to a previously administered agent are not eligible.

Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

Exceptions to this criteria are:

- *Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.*

3.2.8 **Patients receiving palliative radiation are eligible for this study. Palliative radiation is allowed during treatment as well.** Patients with a known additional malignancy that is progressing or requires active treatment within the past 5 years are excluded. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

3.2.9 Patients with a known active central nervous system (CNS) metastases and/or carcinomatous meningitis are excluded.

Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

3.2.10 Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs) are excluded.

Note: Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.11 Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis are excluded.

3.2.12 Patients with an active infection requiring systemic therapy are excluded.

3.2.13 Patients with a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator are excluded.

3.2.14 Patients with a known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial are excluded.

3.2.15 Patients who are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment are excluded.

3.2.16 Patients who have received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent are excluded.

3.2.17 Patients with a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) are excluded.

3.2.18 Patients with a known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected) are excluded.

3.2.19 Patients who have received a live vaccine within 30 days of planned start of study therapy are excluded.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.2.20 Patients with clinically significant cardiac disease (New York Heart Association, Class III or IV (Refer to Appendix 2) including pre-existing arrhythmia, uncontrolled angina pectoris, and myocardial infarction 1 year prior to registration, or grade 2 or higher compromised left ventricular ejection fraction are excluded.

3.2.21 Patients who have dementia or altered mental status that would prohibit informed consent are excluded.

4. TREATMENT PLAN

4.1 Overview

In the Phase 2 study, patients with advanced pancreatic adenocarcinoma who experienced disease progression or did not tolerate first-line therapy, will be treated with pelareorep and pembrolizumab. Pelareorep will be given at a dose of $4.5x10^{10}$ $TCID_{50}$ over 60 min on Days 1, 2, 3 and 8 in Cycle 1 only. From Cycle 2 it will be given on Days 1 & 8 (starting after completion of pembrolizumab infusion) (Table 2). Pembrolizumab at a dose of 200 mg flat dose administered as an intravenous infusion over 30 minutes on Day 1 (Table 2). Each cycle is 21 days (3 weeks). Up to 32 cycles of pembrolizumab and 24 months of Pelareorep (2 years) therapy can be administered. Patients will be followed up for a period of 2 years.

4.1.1 Premedication

No premedication is necessary.

However, regarding Pelareorep, acetaminophen *may be used* for the prophylaxis or treatment of the flu-like signs and symptoms especially fever, that are commonly associated with Pelareorep. Given the usual timing of fever and other "flu-like" adverse events associated with Pelareorep, treatment with acetaminophen should be limited to the days on which Pelareorep is administered and the day following the last dose of each cycle. If used for prophylaxis, it is recommended that the first dose be given 1 to 3 hours following completion of Pelareorep infusion on Day 1 of the cycle. Management of symptoms should take place as necessary (refer to supportive care section 4.4.2).

Note: The decision about using acetaminophen should be considered for each individual patient, with particular attention to the patient's hepatic status at the time of entry into the trial. Extra caution should be used if there is a history of viral (HBV or HCV) hepatitis and/or a pre-entry elevation of bilirubin above normal. If the patient has metastatic cancer in the liver, the impact of the metastases on overall liver function should be considered. If the values for AST and ALT are less than twice the upper limit of normal, acetaminophen may still be used, but careful monitoring of hepatic function should be done.

Dosing of acetaminophen: The recommended dose is 500 (every 6 to 8) to 1000 mg (every 8 hrs). The MAXIMUM daily (24-hour) dose must NOT exceed 3000 mg.

Note: Given that there are more than 600 products that contain acetaminophen, it is also essential that patients be warned NOT to use other products containing acetaminophen at the same time.

4.2 Treatment Administration

Table 2. Treatment administration

Dose Level	PELAREOREP $4.5x10^{10}$ $TCID_{50}$	Pembrolizumab 200 mg	Premedication
Cycle 1	Days 1,2,3,8	Day 1	acetaminophen [1]
Cycle 2 +	Days 1, 8	Day 1	acetaminophen [1]

[1] Given the usual timing of fever and other "flu-like" adverse events associated with PELAREOREP, treatment with acetaminophen should be limited to the days on which PELAREOREP is administered and the day following the last dose of each cycle (Refer to Section 4.1.1).

4.2.1 Pembrolizumab

- Pembrolizumab will be administered first, BEFORE Pelareorep infusion.
- Pembrolizumab does not require any pre-medications unless clinically indicated for an infusion reaction.
- Medications should be available at the bedside per institutional guidelines, in case an immune-mediated reaction should occur.
- Refer to Section 4.4.1 for supportive care details
- Pre-treatment assessment of hydration before each infusion is to be done. Patients must be instructed to adequately hydrate prior to each study treatment dose administration by drinking water and other liquids.
- Pembrolizumab 200 mg will be administered as a 30-minute intravenous (IV) infusion every 3 weeks. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion duration is 30 minutes: -5 min/+10 min).
  - ***Dose modifications for pembrolizumab will not permitted in this study***
- Vital signs (i.e., blood pressure, temperature, heart rate) will be charted starting prior to pembrolizumab immunotherapy

4.2.2 Pelareorep

- Pelareorep infusion should be given after completion of pembrolizumab infusion.
- It should be administered intravenously after appropriate premedication, as needed (Refer to Section 4.1.1)
- Pre-treatment assessment of hydration before each infusion is to be done. Patients must be instructed to adequately hydrate prior to each study treatment dose administration by drinking water and other liquids.
- PELAREOREP will be given at a dose of $4.5x10^{10}$ $TCID_{50}$ over 60 min (+/-15 mins) on Days 1, 2, 3 and 8 in Cycle 1 only. From Cycle 2 it will be given on Days 1 & 8 (starting after completion of pembrolizumab infusion).
  Note: dose modifications are not permitted in this study.
- *Note: All materials that come into contact with Pelareorep viral preparation should be placed in sodium hypochlorite (800 ppm chlorine) and disposed of as biohazardous waste.*
- ***Missed dose:*** Dose delays of Pelareorep for > 7 days will be considered a missed dose and will not be replaced.

4.2.3 **Second Course Phase (Retreatment Period)**

Subjects who stop study therapy with SD or better may be eligible for up to one year of additional pelareorep and pembrolizumab therapy if they progress after stopping study treatment. ***Patients must meet the criteria outlined below prior to starting this re-treatment phase. Re-treatment must be approved by PI and QAM.***

This retreatment is termed the **Second Course Phase** of this study and is only available if the study remains open and the subject meets the following conditions:

- Either:
  - Stopped initial study treatment after attaining an investigator-determined confirmed CR according to RECIST v 1.1, **AND**
    - Was treated for at least 24 weeks with pelareorep and pembrolizumab before discontinuing therapy
    - Received at least two treatments with pelareorep and pembrolizumab beyond the date when the initial CR was declared, **OR**
  - Had SD, PR or CR and stopped Pelareorep and pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability, **AND**
- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment
- Did not receive any anti-cancer treatment since the last dose pelareorep and pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 3.1.8
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received study therapy. Treatment will be administered for up to one additional year.

4.3 Toxicity Management & Dose Delays/Modifications

4.3.1 **Safety Evaluations**

Safety visits will be performed during Cycle 1 on Day 15. It is mandatory for Cycle 1. Beyond cycle 1 it will be done only if clinically indicated, at the discretion of the treating physician (Refer to section 5.0 study procedures table for details).

4.3.2 **Dose delays/ modifications**

No dose reductions for pembrolizumab or pelareorep are allowed in this phase 2 trial.

Note: A cycle can be delayed, but will not be skipped.

For Pelareorep: Pelareorep dose can be held for 7 days. Dose delays of Palereorep for > 7 days will be considered a missed dose and will not be replaced. Patients that have missed Pelareorep for > 6 weeks will be removed from study.

For Pembrolizumab: Dose can be delayed for significant immune AEs but no dose reductions are permitted. Treatment with pembrolizumab can be withheld for up to 12 weeks.

Toxicities MUST be managed as described in the pembrolizumab (Keytruda) package insert instructions for toxicity management [2] and/or Investigator's brochure (IB).

Treatment should be withheld for any of the following:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Symptomatic hypophysitis
- Grade 2 nephritis
- Grade 3 hyperthyroidism
- Grade 2 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 3-5 x upper limit of normal (ULN) or Grade 2 total bilirubin 1.5-3 x ULN (in patients who had normal baseline LFTs)
- AST/ALT ≥8 <10 X ULN (if had elevated AST/ALT with liver metastasis at baseline).
- Any other severe or Grade 3 treatment-related adverse reaction
    - Treatment will resume in patients whose adverse reactions recover to Grade 0-1. Treatment with pembrolizumab can be delayed for up to 12 weeks.
    - *Exception: For any laboratory value that is a Grade 3 adverse event which is expected and unrelated, patient can continue to be treated*
    - *I) if it is in the best interest of the patient 2) following discussion and approval of the PI*

Treatment should be permanently discontinued for any of the following:

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis or recurrent pneumonitis grade 2
- Grade 3 or 4 nephritis
- AST/ALT > 5 x ULN (if patient had normal baseline LFTs)
- AST/ALT ≥ 10 X ULN (if had elevated AST/ALT with liver metastasis at baseline)
- Total bilirubin > 3 x ULN
- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose
- Any severe or Grade 3 treatment-related adverse reaction that recurs
    - *Exception: For any laboratory value that is a Grade 3 adverse event which is expected and unrelated, patient can continue to be treated*
      I) if it is in the best interest of the patient 2) following discussion and approval of the PI

Patients experiencing any toxicity as described in this section in any cycle will have their treatment held until toxicity resolves to baseline or Grade 1. Upon resolution,

pembrolizumab and PELAREOREP, may recommence at the same dose level (i.e., there will be no dose reductions.

4.4 Supportive Care with Pembrolizumab

4.4.1 Supportive care with pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating physician. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids, as well as, additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the treating physician determines the events to be related to pembrolizumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

4.4.1.1 Pneumonitis

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids.
  - Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

4.4.1.2 Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

4.4.1.3 Type 1 Diabetes Mellitus (T1DM)

(If new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

For **T1DM** or **Grade 3-4** Hyperglycemia:

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

4.4.1.4 **Hypophysitis**

- For **Grade 2** events (defined as moderate per general CTCAE criteria), treat with corticosteroids. When symptoms improve to Grade 1 or less (defined as mild per general CTCAE criteria), steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events (defined as either severe or medically significant but not immediately life-threatening, OR life-threatening consequences, per general CTCAE criteria), treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

4.4.1.5 **Hyperthyroidism or Hypothyroidism**

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism:
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

4.4.1.6 **Hepatic**

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly). Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

4.4.1.7 **Renal Failure or Nephritis**

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

4.4.1.8 **SJS and TEN management**

- For signs or symptoms of SJS or TEN, withhold KEYTRUDA® and refer the patient for specialized care for assessment and treatment.
- If SJS or TEN is confirmed, permanently discontinue KEYTRUDA®.

4.4.1.9 **Immune-mediated myocarditis management**

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.

4.4.1.10 **Management of Infusion Reactions:**

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 3 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
	If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.4.1.11 Diet/Activity/Other Considerations

- **Diet**
  Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

- **Use in Nursing Women**
  It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment. Starting with the pre- screening or screening visit through 120 days after the last dose of trial treatment, subjects should not breast feed.

4.4.2 Supportive care for pelareorep

- Flu-like symptoms, such as fever, chills, headache, rhinorrhea, cough, myalgia, arthralgia, and or others may be treated symptomatically with aspirin, acetaminophen, ibuprofen, antihistamines and/or other medications at the discretion of the Investigator.
- Diarrhea may be treated with loperamide (Imodium) or as otherwise deemed necessary by the Investigator. Nausea and vomiting may be treated with metoclopramide or 5HT3 receptor antagonists or as deemed necessary by the Investigator.
- Breastfeeding precautions in Pelareorep: breast feeding patients are excluded from this study.

4.5 Concomitant Medications/Treatments

4.5.1 Permitted

- Supportive and palliative care (e.g. pain control), including palliative radiation, as required throughout the study.
- Corticosteroids (oral or IV) in doses of up to prednisone 1 mg/kg or equivalent for management of pembrolizumab-related immune adverse events.

- Anti-emetics or anti-diarrheal agents as required (see Sections 4.4.1 and 4.4.2).
- Acetaminophen may be used for the prophylaxis or treatment of the flu-like signs and symptoms especially fever, that are commonly associated with PELAREOREP). Given the usual timing of fever and other "flu-like" adverse events associated with Pelareorep, treatment with acetaminophen should be limited to the days on which Pelareorep is administered and the day following the last dose of each cycle .
  Note: Given that there are more than 600 products that contain acetaminophen, it is also essential that patients be warned NOT to use other products containing acetaminophen.
- Concurrent bisphosphonates are allowed.
- The use of erythropoietin will be in strict compliance with FDA recommendations in the current prescribing information.
- The use of blood transfusions is permitted at the discretion of the treating physician.
- Anticoagulant therapy is also permitted.

4.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and PELAREOREP
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the DSMC and PI.

  Note: Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

  The Exclusion Criteria describes other medications which are prohibited in this trial.

4.6 Duration of Therapy

Total duration of therapy on study can be up to 2 years. Patients may continue to receive cycles of treatment until any of the following occur:

- Disease progression
  - *[Note: A subject may be granted an exception to continue on treatment with confirmed or unconfirmed radiographic progression , if clinically stable or clinically improved]*

- Development of an inter-current illness that prevents further administration of treatment
- Intolerable toxicity (that does not respond to either supportive care or dose reduction)
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the as a whole study
- Patients not experiencing clinical benefit in the judgment of the Investigator.
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures).

4.7 Duration of follow-up

- After the end of treatment each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment).
- Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from study therapy for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

  Note: Every effort must be made to contact the treating physicians providing ongoing care to determine whether adverse events occur and to obtain a date of death, if it occurs. This is in order to maximize the safety data obtained from the trial and therefore maximize the safety of future patients treated with PELAREOREP and pembrolizumab

- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed or unconfirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse events
- Intercurrent illness that prevents further administration of treatment
- Investigator’s decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up

- Completed 24 months of uninterrupted treatment with Pelareorep and 24 months of uninterrupted treatment with pembrolizumab or 32 administrations with pembrolizumab, whichever occurs later.

  The patient will be withdrawn from the study and the standard 30 day follow up visit after receiving their last dose will take place.
  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in 4.2.3.

- Administrative reasons

A subject will be discontinued from all study procedures for any of the following reasons:

- Death
- Withdrawal of consent
- Confirmed lost to follow up-Lost to follow-up is defined as 3 attempts made by chosen method of contact.

4.9 Patient Replacement

- If a patient withdraws consent or drops out before 1st evaluation, patient is only evaluable for toxicity. An additional patient will be added for response evaluation.
  - However, if patient drops out before 1st scan due to clinical progression, they are evaluable and an additional patient will not be added for response evaluation.
- If a patient drops out for toxicity related to study drug before 1st evaluation, patient is evaluable for toxicity. An additional patient will be added for response evaluation.
- If a patient drops out after signing consent and before receiving any study drug, this patient will be replaced.

4.10 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with the study therapy and had at least two treatments with PELAREOREP and pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional study treatment via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pelareorep and pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

5. STUDY PROCEDURES

		Cycle 1 (Day 1 of each cycle has a +/- 3 day window)					**Cycles 2, 3, 4 +** (Day 1 of each cycle has a +/- 3 day window)				**End of Treatment** ≤30 days (+/-1 wk)	**Follow-Up** Q3 months[20] (+/-1 month)	**Re-Treatment** (second course phase)[21]
Test/Procedure/Treatment	**Baseline** (-14 days)[1]	**D1**	**D2**[24]	**D 3**	**D 8**	**D15**[22]	**D1**	**D2**[24]	**D8**	**D15**[22]			
Medical History	X												
Physical[2]	X	X[11]			X	X	X[11]		X		X		
Demographics	X												
Height	X												
Weight	X	X					X				X		
Performance status (ECOG)	X	X			X	X	X		X		X		
Toxicity assessment	X[3]	X	X	X	X	X	X	X	X		X		
Vital signs[4]	X	X	X	X	X	X	X	X	X		X		
Hematology, PT/INR/PTT[5]	X	X[11,23]			X	X	X[11,23]		X		X		
Chemistries and special tests[6]	X	X[11,23]			X	X	X[11,23]		X		X		
Thyroid tests[7]	X	X[11,23]											
ACTH [8]	X	X											
CA 19-9[25]		X					X[25]				X		
Urinalysis[9]	X	X[11,23]					X[11,23]				X		
HIV/Hepatitis[10]	X												
ECG[13]	X												
Pregnancy test[12]	X	X[12,23]											
Tumor evaluation[14]	X[1]						X				X	X[14]	
Tumor blocks (if available)[15]	X												
Biopsy[16]	X[16]					X[16]							
Concomitant medications	X	X			X	X	X		X		X		
T cell clonality assay/immune analysis[17]		X			X		X				X		
Pelareorep[18]		X	X	X	X		X		X				X[21]
Pembrolizumab[19]		X					X						X[21]

Note: Each cycle is 3 weeks (21 days). Up to 32 cycles of pembrolizumab and 24 months of Pelareorep (2 years) of therapy can be administered.

[1] Within 2 weeks (14 days) of registration, unless otherwise noted. Baseline imaging can be done within 21 days before registration.

[2] Every physical exam will be a full physical exam and will be standard of care

[3] For Pre-Study visit, toxicity assessment is the recording of baseline signs and symptoms.

[4] Vital signs (i.e., blood pressure, temperature, heart rate) will be charted prior to pembrolizumab immunotherapy, prior to Pelareorep infusion, and 60 minutes (+/-15 mins) after the end of the Pelareorep infusion on Day 1 for all cycles; prior to Pelareorep infusion and 60 minutes (+/-15 mins) after the end of Pelareorep infusion on Cycle 1 Day 2, Day 3, and Day 8. From Cycle 2 onwards, vitals will be charted prior to pembrolizumab immunotherapy, prior to Pelareorep infusion, and 60 minutes (+/-15 mins) after the end of the Pelareorep infusion on Day 1 for all cycles; prior to Pelareorep infusion and 60 minutes (+/-15 mins) after the end of Pelareorep infusion on Day 8.

[5] Hemoglobin, hematocrit, RBC, WBC with differential count, platelets. In addition, coagulation tests which includes INR or PT and PTT will be done.

[6] Electrolytes (sodium, potassium, calcium); Renal function (blood urea nitrogen (BUN) and creatinine); Liver function (total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase) and others (glucose).
Additional special tests: magnesium, uric acid, direct bilirubin, GGT and LDH.

[7] Thyroid tests: TSH with reflex T3 and T4. Thyroid function will be evaluated at baseline (performed within 14 days of registration) and prior to the start of the next treatment cycles e.g. 4, 7, 10, etc.

[8] Endocrine test ACTH to be done at baseline. If the test is not done at baseline, it should be done on C1D1 (for both instances, it DOES NOT need to be resulted for treatment to start) Physician may repeat it during the study, if there is clinical evidence of hypopituitarism or adrenal dysfunction.

[9] Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, microscopic, and nitrite

[10] HbsAg, anti-HCV testing and HIV virus testing to be done at baseline.
Note: If patient had a hepatitis screening done > 14 days and < 30 days from registration, then it does not need to be repeated.
Note: If history of HIV is positive and test results (antibodies HIV1 and HIV 2) are available, then HIV testing is not required at baseline.

[11] These tests (physical exam, hematology, chemistry, thyroid tests, and urinalysis) must be done within 3 days of the start of treatment on Day 1 of each cycle. *Note: For Cycle 1 only, these procedures and labs can be eliminated if baseline procedures and labs were done within 3 days of the start of treatment on Cycle 1 Day 1*.

[12] Pregnancy test within 7 days of study treatment for females of child bearing potential. If urine test is positive then a serum pregnancy test is required. It is to be repeated on C1 Day 1 before infusion, if done more than 3 days prior to Day 1.

[13] ECG will be performed at baseline. It may be performed in subsequent visits if clinically indicated.

[14] Baseline tumor assessment with full trunk CT or MRI scanning (as appropriate), including a brain MRI if clinically indicated and per treating physician's discretion. Baseline imaging can be done within 21 days before registration. CT and/or MRI will also be performed the last week of Cycles 3, 6, 9 (+/-7 days), etc. (Every 3 cycles [+/-7 days]).
For patients that discontinued due to toxicity, tumor evaluations should be performed until PD is noted.

[15] If available, archival tissue from diagnosis (FFPE) will be acquired for immune testing.

[16] If archival tissue is not available, then a baseline biopsy of a primary or metastatic lesion (including ascites) which is accessible for either direct or needle biopsy is to be done within 14 days of registration.
Post treatment biopsy will be performed on Cycle 1 between Day 4 and Day 15.

[17] Blood sample for T cell clonality/immune analysis on C1D1, C1D8, C2D1, C3D1, C4D1 and EOT.
Note: This blood sample is for correlative studies. The sample will be stored at NU biorepository, to be analyzed at a later date.

[18] Pelareorep will be given at a dose of 4.5x1010 TCID50 over 60 min on Days 1, 2, 3 and 8 in Cycle 1 only. From Cycle 2 it will be given on Days 1 & 8 (starting after completion of pembrolizumab

infusion) (Table 2). Dose delays of Pelareorep for > 7 days will be considered a missed dose and will not be replaced. Pre-treatment assessment of hydration before each infusion is to be done. Patients must be instructed to adequately hydrate prior to each study treatment dose administration by drinking water and other liquids.

[19] Pembrolizumab will be administered on Day 1 of each cycle (before pelareorep infusion) at 200 mg IV over 30 minutes. Pre-treatment assessment of hydration before each infusion is to be done. Patients must be instructed to adequately hydrate prior to each study treatment dose administration by drinking water and other liquids.

[20] Follow-up Visits every 3 months by a telephone call or clinic visit at the discretion of the investigator. These visits or phone calls are to determine survival outcome.
Note: Follow-up will be for a maximum of 2 years.

[21] Subjects who stop study therapy with SD or better may be eligible for up to one year of additional pelareorep and pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets certain conditions as outlined in the protocol (See section 4.2.3).
Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received study therapy. Treatment will be administered for up to one additional year.

[22] D15 is a safety visit. It is mandatory for Cycle 1. Beyond cycle 1 it will be done only if clinically indicated, at the discretion of the treating physician.

[23] All Day 1 labs (except ACTH and CA 19-9) to be resulted before study drug administration.

[24]D2 visit is mandatory only for Cycle 1. Beyond Cycle 1 it is optional and will be done only if clinically indicated, at the discretion of the treating physician.

[25] Blood test for CA 19-9 will be done at baseline, D1 of each odd numbered cycle (e.g C3D1,C5D1 etc) and at EOT visit. This is a standard of care test. *(Note:The test need not be resulted for treatment to start).*

6. ENDPOINTS AND ASSESSMENTS

Response assessments will be made using the RECIST v1.1 criteria. Measurable and non-measurable lesions are defined below. Disease progression will be determined using RECIST v 1.1 criteria. The iRECIST criteria will be used for exploratory endpoints.

Below is a summary of the RECIST version 1.1 guidelines as a quick reference that can be utilized for this study. If there are items not outlined below, further detail and clarification for RECIST 1.1 can be obtained from the European Journal of Cancer, 2009.45:p.228-247, by Eisenhaur, et al.

Comparison of RECIST 1.1 and iRECIST can be obtained at:

"iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics" Seymour, et al (**Volume 18, No. 3**, e143–e152, March 2017) (http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30074-8/fulltext

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

6.1 Definitions

Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

- **Measurable Disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable Lesions** - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10mm by CT scan (CT scan slice thickness no greater than 5 mm.
  - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be rescored as non-measureable).

- 20 mm by chest x-ray

- **Nonmeasurable Lesions** - all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis as well as truly non-measureable lesions. Lesions considered truly non-measurable lesions. Lesions considered truly non-measurable include; leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

  All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

6.2 Methods of Measurement

- CT and MRI: CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols. See RECIST v1.1 guidelines for additional specifications on CT and MRI measurements.
- Chest X-ray: Chest CT is preferred over chest x-ray; particularly when progression is an important endpoint, since CT is more.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is a concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy and Laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised.
- Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

6.3 Baseline Documentation of Target and Non-Target Lesions

- When more than one measureable lesion is present at baseline all lesions up to a maximum of five (5) lesions total (and a maximum of two (2) lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.
- Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. To be identified as target lesions lymph nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. See RECIST v1.1 guidelines for further detail.
- A sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor regression in the measurable dimension of the disease.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Table 4 - Time point response: patients with target (+/- non-target) disease.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease, and NE = inevaluable

Table 5 - Time point response: patients with non-target disease only.

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable

6.4 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including baseline if that is the smallest). In addition, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on

study. SD criteria must have been met at least once after study entry at a minimal interval (in general not less than 6-8 weeks).

- *Note: Target lesions (e.g. lymph nodes) that become too small to measure but still visible should be assigned a default value of 5 mm (derived from CT scan slice thickness).*
- *Note: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.*
- *Note: The finding of "New Lesion" should be unequivocal, i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (e.g. some new bone lesions may be simply healing or flare of pre-existing lesions; or necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion. This may be particularly important when there is evidence of CR or PR in target lesions.*

6.5 Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
- Non CR/Non PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. Appearance of one or more new lesions is also considered progression.
- *Note: While some non-target lesions may actually be measurable, they need not to be measured and instead should be assessed only qualitatively at the time points specified in the protocol.*
- *Note: A modest increase in one or more non-target lesion(s) is usually not sufficient to qualify as unequivocal progression. The designation of overall progression solely on the basis of change in the non-target disease in the face of SD or PR of target lesions will therefore be extremely rare.*

6.6 Overall Response Evaluation

See Tables 4 and 5 (Section 6.3).

6.7 Immune-related response criteria [1]

The principles used to establish objective tumour response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumour shrinkage. iRECIST defines iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (i.e., target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterized.

*(Reference: iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics" Seymour, et al (**Volume 18, No. 3**, e143–e152, March 2017) [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30074-8/fulltext])*

Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint. “i” indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response EvaluationCriteria in Solid Tumours.

- For the immune-related response criteria, measurable new lesions are taken into account. For tumor assessmenttwo lesions per organ, up to 5 visceral lesions are calculated. Measurable Lesions are lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
    - 10mm by CT scan (CT scan slice thickness no greater than 5 mm.
    - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be rescored as non-measureable).
    - 20 mm by chest x-ray

  [2 new lesions per organ, upto 5 visceral lesions)provide the total tumor burden]

Formula for tumor burden: $SPD_{index}+SPD_{new}$

1. irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions), confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

2. irPR, decrease in tumor burden ≥50% relative to baseline, confirmed by a consecutive assessment at least 4 wk after first documentation.

3. irSD, not meeting criteria for irCR or irPR, in absence of irPD.

4. irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden), confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

6.8 Primary Endpoint

To determine the overall response rate (ORR) by RECIST v 1.1 criteria for the combination of pembrolizumab with Pelareorep.

To address the primary objective, 2 or more responses (CR or PR) out of 11 are needed in Stage 1 to continue the trial to the full 30 patients. If the trial continues to the full 30 patients. Then ORR will be estimated using a two stage method.

Evaluable patient: A patient needs to have taken one dose of either study drug, and completed the first scan to be evaluable for this primary endpoint.

Note: If a patient drops out of the study before the first scan, due to clinical progression, they are evaluable and will not be replaced.

6.9 Secondary Endpoints

To determine progression free survival by RECIST v1.1 criteria, as well as 1-year, 2-year and median overall survival with pembrolizumab in combination with Pelareorep.
Evaluable patient: Any patient who has taken one dose of either study drug will be evaluable for this endpoint.

2.To determine safety and tolerability of pembrolizumab and pelareorep when administered in combination as determined by NCI CTCAE v 4.03.

Evaluable patient: Any patient who has taken one dose of either study drug will be evaluable for this toxicity endpoint.

3. To determine the effects (immune response) of pembrolizumab and pelareorep when administered in combination as determined by analysis of pre-and post- treatment biopsies and blood-based immune markers.

Evaluable patient: Any patient who has taken one dose of both study drugs and has given the pre-dose and atleast one post dose blood and/or tissue samples will be evaluable for this toxicity endpoint.

6.10 Exploratory Endpoints

To measure the overall response rate (ORR) by using iRECIST criteria, for the combination of pembrolizumab and Pelareorep

To determine progression free survival by iRECIST criteria, as well as 1-year, 2-year and median overall survival with pembrolizumab in combination with Pelareorep

6.11 Assessment of Antineoplastic Activity

Patients will be assessed by CT or MRI following the RECIST Guidelines (version 1.1)]. Tumor measurements will be performed at baseline (on cycle 1 day 1 or up to 7 days before study treatment initiation) and every 3 weeks thereafter (Appendix 4). Tumor assessments will be performed with RECIST1.1 criteria

Post treatment scans should be performed every 3 months after treatment ends (if patient has not progressed during treatment) and repeated until the patient has progressed. Confirmation of a complete or partial response (CR or PR) is required with repeat imaging 4 weeks after criteria of response first met.

7. ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study requires high intensity monitoring as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.
- If an AE remains unresolved at the conclusion of the study, the investigator and DSMC will make a clinical assessment whether continued follow-up of the AE is warranted.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should

reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

The Investigator is responsible for ensuring that all AEs identified during the reporting period are followed until they are resolved or until they become chronic with no resolution expected. Follow-up of all AEs must be documented in the patient's medical record and on the CRF.

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 90 days after the last administration of study drug, must be reported upon discovery or occurrence. Please refer to section 7.4 for protocol specific additional requirements to SAE reporting.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in death.**
  - If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- **Is life-threatening.**
  - The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly/birth defect.**
- **Is an important medical event.**
  - Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
  - For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to Oncolytics and Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to Pelareorep and/or pembrolizumab, must be reported within 24 hours to QA/DSMC and within 2 working days to Merck Global Safety and Oncolytics.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Pelareorep and or pembrolizumab that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to QA/DSMC, Oncolytics and to Merck Global Safety.

All subjects with SAEs must be followed up for outcome.

7.2.3 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness, as required by both Merck and Oncolytics.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1. Identify the type of adverse event using the NCI CTCAE v 4.03[3].
2. Grade the adverse event using the NCI CTCAE v 4.03[3].
3. Determine whether the adverse event is related to the protocol therapy.
    a. Attribution categories are as follows:
        i. Definite: AE is clearly related to the study treatment.
        ii. Probable: AE is likely related to the study treatment.
        iii. Possible: AE may be related to the study treatment.
        iv. Unlikely: AE not likely to be related to the study treatment.
        v. Unrelated: AE is clearly NOT related to the study treatment.
4. Determine the prior experience of the adverse event.
    a. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
        i. the current protocol
        ii. the drug package insert
        iii. the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the Oncolytics SAE Form for Oncolytics and NU SAE form for QA/DSMC and Merck, provided as a separate documents, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 **Reporting to the FDA**

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 **Reporting to Oncolytics Biotech Inc and Merck**

SAE reports and any other relevant safety information are to be forwarded to the Global Safety facsimile number: +1-215-993-1220 for Merck and sae_reports@oncolytics.ca or 403-283-0858 for Oncolytics.

The NU SAE form is to be used for reporting to Merck and the Oncolytics SAE form is to be used for reporting to Oncolytics.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators are required to cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators are required to submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) for Merck and sae_reports@oncolytics.ca or 403-283-0858 for Oncolytics, at the time of submission to FDA.

7.4 Protocol-Specific Additional Reporting Requirements for Serious Adverse Event Reporting

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study. Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

7.4.1 Events of Clinical Interest

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to DSMC and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220).and Oncolytics at sae_reports@oncolytics.ca or 403-283-0858

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to DSMC and within 2 working days to Merck Global Safety and Oncolytics if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Pelareorep and or pembrolizumab, must be reported within 24 hours to DSMC and within 24 hours to Merck Global Safety and Oncolytics

Events of clinical interest for this trial include:

- an overdose of Merck product, as defined in Section 7.4.3 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
- **Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.*

7.4.2 **Management and Reporting of Pregnancy**

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial. The pregnancy is to be immediately reported to QA/DSMC, Oncolytics Biotech Inc., and Merck & Co Inc. Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of any of the study drugs, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. The anticipated date of birth or termination of the pregnancy should be provided at the time of the initial report. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, stillbirth and neonatal death occurring ≤ 30 days after birth must be reported as SAEs. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

The Investigator must follow the procedures outlined in protocol Section 7.3.3 for reporting SAEs. Such events must be reported within 24 hours to QA/DSMC and

Oncolytics (sae_reports@oncolytics.ca or 403-283-0858), and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220). The outcome of the pregnancy should be reported to Oncolytics Biotech Inc. and Merck & Co Inc. as soon as it is known. If the pregnancy ends for any reason before the anticipated date initially reported the Investigator should notify Oncolytics Biotech Inc. and Merck & Co Inc. the following working day.

7.4.3 **Definition of an Overdose of Pembrolizumab for This Protocol and Reporting of Reporting of Overdose to QA/DSMC and Merck**

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."
All reports of overdose with and without an adverse event must be reported within 24 hours to QA/DSMC and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

8. DRUG INFORMATION

8.1 Pembrolizumab

8.1.1 **Other names**

MK-3475, KEYTRUDA

8.1.2 **Classification and type agent**

Humanized monoclonal antibody against PD-1 protein.

8.1.3 **Mode of action**

Highly selective anti-PD-1 humanized monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling (Hamid, 2013). Anti-PD-1 antibodies (including pembrolizumab) reverse T-cell suppression and induce antitumor responses.

8.1.4 **Storage and stability**

Please refer to pharmacy manual for detailed instructions.
Pembrolizumab is provided as a white to off-white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only.

Pembrolizumab powder for solution for injection is a sterile, non-pyrogenic lyophilized powder for intravenous infusion supplied in single-use glass vial containing 50 mg of pembrolizumab. The product is preservative-free, white to off-white powder, and free from visible foreign matter.

Pembrolizumab solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab. The product is preservative-free, latex free solution which is essentially free of extraneous particulates. Pembrolizumab solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0mL (100mg).

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Pembrolizumab vials should be stored a refrigerated conditions (2°C to 8°C). Do not freeze; do not shake. Prior to reconstitution, the vials of lyophilized powder can be out of refrigeration (temperatures at or below 25°C (77°F) for up to 24 hours.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.1.5 **Protocol dose specifics**

Pembrolizumab 200 mg will be administered as a 30-minute intravenous (IV) infusion every 3 weeks. Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion duration is 30 minutes: -5 min/+10 min).

Dose modifications to pembrolizumab will not permitted in this study

8.1.6 **Preparation**

- Pembrolizumab powder for solution for Infusion is reconstituted with 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.
- Limit the number of punctures of each vial to two (one for reconstitution, one for withdrawal)
- Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Reconstituted Pembrolizumab is a clear to slightly opalescent, colorless to slightly yellow solution. Discard reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.
- Reconstituted vials and pembrolizumab infusion solutions are to be further diluted to final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Withdraw the required volume from the vials of Pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. Mix diluted solution by gentle inversion 10-15 times to mix the solution.
- If normal saline is not available, 5% Dextrose Injection, USP or regional equivalent (5% dextrose) is permissible, Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.
- The bag must be filled to at least 30% of its capacity
- Pembrolizumab should not be mixed with other diluents.

- Discard any unused portion left in the vial. The product does not contain a preservatives.
  Store the reconstituted and diluted solutions of Pembrolizumab either:
- At room temperature for no more than 4 hours from the time of reconstitution. The 4 hour countdown begins when the vial is pierced, and includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion.
- IV bags and/or reconstituted vials can be also stored refrigerated at 2—8 degrees ^{0}C (36—46 degrees ^{0}F) for up to 20 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Do not freeze.

8.1.7 **Route of administration**

- Administer infusion solution intravenously over 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter, using a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. Pembrolizumab 200 mg will be diluted in 50 or 100 ml NS.
- Do not co-administer other drugs through the same infusion line.
- Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered according to institutional guidelines for saline flushing.

8.1.8 **Incompatibilities**

The following infusion bag materials are compatible with pembrolizumab (MK-3475): PVC plasticized with DEHP, Non-PVC (polyolefin), EVA, PE lined polyolefin.

8.1.9 **Availability & Supply**

Clinical Supplies will be provided by Merck as summarized in Table below. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements

Product Descriptions

Product Name & Potency	Dosage Form
Commercial Keytruda 100 mg/ 4mL	Liquid for infusion

Merck will supply pembrolizumab directly to the NU Investigational Pharmacy at no charge to subjects participating in this clinical trial. The contact for drug ordering will be Debra Perlow (debra.perlow@merck.com) or Tammy Moll (:tammy.moll@merck.com). The Merck Drug Request Form, provided by Merck, should be completed and emailed to these contacts. It is imperative that only drug product designated for this protocol number be used for this study. Drug is protocol specific, but not patient specific

Clinical Supplies Disclosure of pembrolizumab
This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.1.10 **Side effects**

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern.

Important identified risks for pembrolizumab are of an immune mediate nature, including:

- pneumonitis
- colitis
- thyroid disorders (hypothyroidism/hyperthyroidism)
- hepatitis
- hypophysitis
- Type I diabetes mellitus
- uveitis, and
- nephritis

After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction; these are included in the reference safety information in the current IB. The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

Please refer to current IB for a complete list of side effects.

8.1.11 **Safety and monitoring plan**

All participants will be carefully followed for safety. Safety evaluations include a physical exam, vital signs, performance status assessment, and safety laboratory tests. Medications should be available at the bedside per institutional guidelines, in case an immune-mediated reaction should occur.

8.1.12 **Return and Retention of Pembrolizumab**

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused pembrolizumab vial(s) shall be returned to the designated facility for destruction.
Please refer to pharmacy manual for the address of the designated facility.

All used and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8.2 PELAREOREP

8.2.1 **Other names**

REOLYSIN®

8.2.2 **Classification - type of agent**

Reovirus® Serotype 3 – Dearing Strain

Double-stranded RNA; icosahendric; no envelope,70nm

8.2.3 **Mode of action-**
Pelareorep is an isolate of reovirus type 3 Dearing. Pelareorep contributes to cell lysis through selective viral replication and promotes anti-tumor immunity through activation of NK cells and adaptive immune response.

8.2.4 **Storage and stability**
Please refer to pharmacy manual for detailed instructions.

Pelareorep is a clear to translucent, colorless to light-blue liquid containing up to $3x10^{11}$ $TCID_{50}$ of Reovirus Serotype 3 – Dearing strain per mL. The final formulations of pelareorep will contain designated amounts of $TCID_{50}$ in a phosphate-buffered solution. Most supplied vials will contain $4.5 x10^{10}$ $TCID_{50}$ per 1 mL, but pharmacist should check the label of each individual vial.
Three lots of drug product have been on stability studies for up to 60 months (when stored at -70º C) and viral titre data has been included in the table below. Recent data demonstrates that the Reovirus remains active when stored at ≤-20ºC. . Before distribution to the sites, PELAREOREP will continue to be stored at ≤-70ºC Updated stability information will be provided as additional data is collected. PELAREOREP should be stored at ≤-20 ºC or ≤-60 ºC within the cryobox or carton to protect from light. The drug storage should not be switched between ≤-20 ºC and ≤-60 ºC, and the supply should be maintained at one temperature.

8.2.5 **Protocol dose specifics**
No premedication is necessary. PELAREOREP will be given over 60 min mins at a dose of $4.5x10^{10}TCID_{50}$ IV daily on Days 1, 2, 3 & 8 of Cycle 1 (starting after completion of pembrolizumab infusion on day 1). From Cycle 2 onwards pelareorep at a dose of $4.5x10^{10}TCID_{50}$ IV daily will be administered on Days 1 and 8.
The treatment cycle will be repeated every 21 days.

8.2.6 **Preparation**
When removing the drug from its original shipment box, wear gloves and face shield or safety glasses.

When preparing pelareorep inside the biosafety cabinet or Barrier-Isolator, wear appropriate personal protective equipment per protocol requirement or wear standard PPE of impervious smart sleeve gown, powder-free sterile gloves, and surgical mask (wear face shield or safety glasses if there is a risk of splashing).

When transporting the drug to the final patient care area and when the drug is in a secured secondary container, wearing of PPE is not required.

When cleaning biosafety cabinet, wear surgical mask, impervious gown, double gloves (i.e. nitrile), and protective eyewear (also wear a face shield if there is a risk of splashing).

When handling spill cleanup or removing/ handling waste containers, wear double gloves (i.e. nitrile), impervious gown, mask, and protective eyewear (also wear a face shield if there is a risk of wear of splashing).

Pelareorep is a clear to translucent, colorless to light-blue liquid containing up to $3x10^{11}$ $TCID_{50}$ of Reovirus Serotype 3 – Dearing strain per mL. The final formulations of pelareorep will contain designated amounts of $TCID_{50}$ in a phosphate-buffered solution.

Prior to clinical use, the test drug will be prepared by the pharmacy. Pelareorep will be thawed and diluted to the appropriate concentration using 0.9% Sodium Chloride Injection, EP. Time from the thawing and dilution process to administration to the patient must be less than 7 hours (plus 1 hour of infusion) and a detailed Drug Handling Guideline/Pharmacy Manual will be provided to the investigation sites for the process. Reovirus is known to be a very stable and resistant virus in the environment and there are no concerns with maintaining the thawed and diluted virus for up to 8 hours under these conditions.

Purified pelareorep will be provided to the pharmacy at each study site in glass vials. The dilution or mixing will be done by the pharmacy at the study sites. Vial labels will indicate the product, lot number and concentration. The procedure will be undertaken with appropriate precautions including mask, gown and gloves. The procedure will be undertaken in a specifically prepared biological safety cabinet under aseptic conditions. The dose will be prepared by a pharmacist. Drug Handling Guidelines/Pharmacy manual will be provided for each batch with specific manipulation instructions. **Pelareorep must be stored at ≤ -20ºC in glass vials (1 mL volume). If preferred, it is acceptable for sites to continue to store product as previously recommended at ≤-60 ºC.**

The prepared Pelareorep infusion must be kept refrigerated at 2-8 ºC up to 7 hours (prior to 1 hour infusion at room temperature) or at room temperature for 30 minutes (prior to 1 hour infusion at room temperature).

Note: All material that comes into contact with the viral preparation will be placed in sodium hypochlorite (800 ppm chlorine) and disposed of as biohazardous waste.

8.2.7 **Route of administration for this study**
Intravenous (IV)

8.2.8 **Incompatibilities**
Please refer to section 4.5.2

8.2.9 **Availability & Supply**
Purified Pelareorep will be provided to the pharmacy at each study site in glass vials.

REOLYSIN® (pelareorep) is a clear to translucent, colorless to light-blue liquid containing $4.5x10^{10}$ $TCID_{50}$ of Reovirus Serotype 3 – Dearing strain per mL. The product is supplied as 1 mL of pelareorep contained within a 2 mL glass vial. The final formulations of pelareorep will contain designated amounts of $TCID_{50}$ in a phosphate-buffered solution.

8.2.10 **Side effects**
Please see current Investigator's Brochure for a complete list of adverse events.

Likely to Occur:

- Mild "flu-like" symptoms such as:
- Fever
- Chills
- Tiredness or general weakness
- Mild gastrointestinal symptoms such as:
    - Nausea
    - Vomiting
    - Diarrhea

Less Likely, some may be serious (occurs in 1-10):

- Mild and transient changes in ALT (SGOT) levels
- **Laboratory abnormalities:**
  - Neutropenia
  - Thrombocytopenia,
  - increased ALT and LDH
  - Proteinuria

Rare, some may be serious (occur in less than 1%):
Patients who receive REOLYSIN® only (no chemotherapy or radiation therapy)

- Temporary effect on liver
- Temporary effect on heart
- Temporary changes in kidney function
- Temporary impairment to eye function
- Hypotension

Please refer to current IB for details on side effects of REOLYSIN in combination with chemotherapy

8.2.11 **Nursing implications**

Please refer to the Pharmacy Manual and the Biosfaety Manual for complete set of instructions for handling, administration and disposal of pelareorep.

A few critical precautions are listed below:

- When connecting / disconnecting tubing, needles or syringes outside of biosafety cabinet, staff need to follow standard precautions including wearing eye protection (safety glasses). Consider wrapping a gauze or alcohol wipe around the luer-lock, syringe, or needle when connecting or withdrawing it from the tubing or connection to prevent droplet contamination if appropriate.
- Pelareorep shall NOT be handled with bare hands.
- Staff must wear double gloves, surgical mask, and protective eyewear whenever opening the secondary and primary container housing pelareorep.
- Observe standard hand hygiene after removing gloves each time.
- When nursing performs specimen collection, double gloves, wear a surgical mask and protective eyewear are required. The precautions taken during administration of the drug should also be taken when drawing blood and collecting other specimens for patients.
- Patients should be instructed to use a designated toilet whenever possible. The facility should be decontaminated after the study subject is released from the treatment area.
- Please refer to Pharmacy Manual for details regarding appropriate drug disposal.
- Pregnant or nursing staff should not administer or handle pelareorep.
- Either a central line or a peripheral line can be used for administration, so long as the line is flushed after the pelareorep infusion.

- Pelareorep on Day 1 will be administered after the end of pembrolizumab infusion.

- Pre-treatment assessment of hydration before each infusion is to be done. Patients must be instructed to adequately hydrate prior to each study treatment dose administration by drinking water and other liquids.

- When discharged, the patient and the family will receive an outpatient information sheet regarding infectious precautions that they should follow both at home and in public [See Appendix 3].

NOTE: These instructions are available in a 'patient information sheet' as stand-alone document

Note: All material that comes into contact with the viral preparation will be placed in sodium hypochlorite (800 ppm chlorine) and disposed of as biohazardous waste.

8.2.12 **Return and Retention of Study Drug**

The Principal Investigator will designate a pharmacist who will be responsible for tracking all pelareorep requested and delivered to the study site and its administration to individual patients. Any unused supply of pelareorep will destroyed on site upon completion of the trial. Oncolytics will provide instructions for the return or destruction of unused product upon the completion of the trial.
All materials that were in contact with the viral preparation will be placed in sodium hypochlorite (800 ppm chlorine) and disposed of as biohazardous waste.
The site investigator is responsible for keeping accurate records of the clinical supplies received from Funders or a designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy.
It is the site Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9. CORRELATIVES/SPECIAL STUDIES

Clinical responses will be correlated with the presence of an "inflamed phenotype" (as detected by gene-expression profile) and the emergence of selective T & B cell clones against tumor- or viral associated antigens after the start of therapy (T cell clonality in blood).

- Patients will have biopsies (or available archival tumor tissue) before treatment initiation and on-therapy (if feasible) between C1D4-C1D15 to assess an inflammatory gene expression profile in the tumor and tumor microenvironment.

- Assays to evaluate adaptive immunity (T cell clonality) will be performed on tumor tissue as well. Biopsies are to be performed if a lesion is easily accessible, the biopsy is not contraindicated and the patient consents.

- Assays to evaluate adaptive immunity on peripheral blood will be performed on C1D1 (before any therapy), C1D8 (before pelareorep infusion) and C2D1, C3D1 and C4D1 before treatment initiation and at end of treatment.

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Correlative Samples			
Correlative study (sample type) *e.g. Pharmacokinetics (blood)*	**Inflammatory gene expression profile (biopsy)**	**Evaluation of adaptive immunity (T cell clonality) [in biopsy]**	**Evaluation of adaptive immunity (T cell clonality) [in blood]**
Mandatory or Optional	mandatory	mandatory	mandatory
Timing (+/- windows)	Archival tissue or biopsy before treatment. Optional 'on therapy biopsy' between C1D4-C1D15	See section 5.0 and lab manual	See section 5.0 and lab manual
Volume Needed (blood only)	N/A	N/A	6mL
Tube type needed (blood only)	N/A	N/A	EDTA
Tissue thickness and/or # slides (tissue only)	See lab manual	N/A	N/A
Processing center	PCF-CTU	PCF-CTU	PCF-CTU
Sample handling/processing instructions	See lab manual	See lab manual	See lab manual
Storage	NU Biorepository	NU Biorepository	NU Biorepository

Please note: Currently, blood samples and tumor samples will be collected and stored and analysis will be done in the future, when adequate resources are available. The above samples will be collected by the PCF-CTU personnel and the samples will be stored in the NU biorepository till further processing and analysis is done. Please see the laboratory manual for detailed sample collection, processing and shipping information.

10. STATISTICAL METHODS

This Phase 2 trial follows a Simon's two-stage design to evaluate the efficacy of pembrolizumab in combination with pelareorep. The "Go/No Go" criteria in Phase 2 (Stage 1) will be defined using null response rate, alternative response rate, power, and alpha. In Stage 1, with null rate 10%, alternative rate 35%, power 90%, and 1-sided alpha 0.025, the Simon two-stage "optimum" design specifies stage 1 sample size of 11, stopping for futility if <= 1 response out of 11 in stage 1, and adding 19 additional patients if >= 2 responses at stage 1. In Stage 2, 7 responses out of 30 are required to reject null rate <10%.

To address the primary objective, >=2 responses out of 11 are needed in Stage 1 to continue the trial to the full 30 patients. If the trial continues to the full 30 patients, then ORR will be estimated using a two stage method (Porcher R, Desseaux K. What inference for two-stage phase II trials. BMC Medical Research Methodology 2012;12:117.) Kaplan-Meier curves will be used to determine 1-year, 2 year and median overall survival. For the secondary objectives, Kaplan-Meier curves will be used to determine 1-year, 2 year and median progression-free survival. These analyses will be done at the end of Stage 1 and Stage 2. Pre- and post-treatment biopsies and immune markers will be assessed for change using paired statistical methods such as paired t-tests or signed rank tests.

11. STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

Amendments to the protocol will be initiated and maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, drug company, or FDA. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by [insert Funding Sponsor name if applicable]. Amendments will be distributed by the lead institution (Northwestern) to all participating sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

For potential patients, study teams are asked to inform the assigned QAM (croqualityassurance@northwestern.edu) of the date and time that the patient will need to be registered.

BEFORE a patient can be treated on study, the following items must be completed and submitted to confirm eligibility and receive a subject identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Copy of the pathology report (upload to NOTIS)
- Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review the registration documents. Once review is complete, he or she will register the patient, assign a subject identification number, provide a cohort assignment (as applicable) and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Data collection for this study will be done through NOTIS. Access to the trial in NOTIS is granted to appropriate roles identified at the time of participating site activation, or upon request. Site users will not be able to access the study in NOTIS until all required and study specific trainings are completed.

Once a patient is confirmed and registered to the study, eCRFs should be submitted according to the study procedures table. Generally, for all phase II/III patients, data are due with 10 days of a visit or end of cycle. A set amount of data may also be requested for any screen failures, as is defined by the study. In most instances, this will include collection

of adverse events and baseline data from the time of registration to the date of screen failure

11.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data and Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires High Intensity Monitoring as outlined in the DSMP. The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level.

11.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.7.2 Other Protocol Deviations

All other deviations from the protocol must be reported in a timely manner to the assigned QAM using the NU CTO Deviation form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.8 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.9 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

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13. APPENDICES

13.1 Appendix 1: Birth control methods

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Male condom plus spermicide • Cap plus spermicide • Diaphragm plus spermicide	• Copper T • Progesterone T • Levonorgestrel-releasing	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

NOTE: choice contraception should be discussed with primary treating oncologist to discuss the risks and benefits of different modalities of contraception.

13.2 Appendix 2: New York Heart Association Classification of Heart Failure (NYHA CHA)

Class	Symptomatology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

13.3 Appendix 3: SAFETY ISSUES

Please note: These instructions will be available as a stand-alone document in the form of a 'Patient Information sheet' and will be submitted to the IRB

Patients will handed a safety precaution sheet with instructions to be followed on study or until the investigator advises otherwise.

Treatment with Pelareorep

What to do while you are on study:
The cancer treatment you are receiving is called PELAREOREP. This new treatment uses a type of virus called Reovirus, a virus commonly found in natural situations throughout the world (such as ponds and ditches). Most adults (up to 100%) have been exposed to Reovirus at some point in their day-to-day life. People exposed to this virus in their community often do not have any symptoms, or occasionally have only very minor breathing or stomach upsets. Even though Reovirus is usually asymptomatic, your study doctor believes that it is appropriate to take some precautions to minimize exposure to Reovirus for individuals in close proximity to you, such as your family.

During the 5 days of PELAREOREP treatment and for up to 2 days afterwards, it is recommended that you adopt the common practices that you would normally observe around family and friends if you had a cold or flu. These include standard behaviors you would use to prevent passing on a cold or flu virus such as:

- washing your hands with soap after using the bathroom,
- avoid sharing drinks and eating utensils,
- using detergent to wash your dishes, either by hand or in a dishwasher,
- avoiding close contact with pregnant women and infants.
- You are also asked to avoid direct contact with severely immune-compromised individuals such as patients who have had a recent bone-marrow transplant or patients with AIDS.

If you have any questions about any of these recommendations please ask your study doctor.

13.4 Appendix 4: Table Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†Results in death; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with

		investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

14. HISTORY OF AMENDMENTS (SUMMARY OF CHANGES)

Amendment 1 –January 23rd , 2019			
Sections(s) Affected	**Prior Version**	**Amendment 1 Changes**	**Rationale**
Section 5 Study procedures table Footnote 24	There was no footnote alongside D2 of each cycle to indicate if it was mandatory or optional	New footnote 24 inserted alongside D2 of each cycle. It states that "D2 visit is mandatory only for Cycle 1. Beyond cycle 1 it is optional and will be done only if clinically indicated, at the discretion of the treating physician"	***To reduce burden on patients and increase flexibility***.
Section 8.2.10 Side effects of Pelareorep	List of some of the known side effects of Pelareorep	A SUSAR was received from Oncolytics. The AE reported was *hypotension.* This has been added to the **"Rare, some may be serious (occur in less than 1%) "category of side effects of Pelareorep.**	***Based on SUSAR received from Oncolytics on 12.4.18 which was submitted as RNI on 12.7.18***
Section 3.1.9 Eligibility criteria	Required patients to have ACTH values within normal range prior to registration. (This required the ACTH test to be resulted before registration) TSH , T4 were required to be within normal range for eligibilty to be met	Removed the requirement for patients to have normal ACTH before registration. (This removes the requirement for ACTH to be resulted before registration. ACTH results will be kept as a baseline and will be followed up as clinically indicated). Inserted a note stating that "If a thyroid function test is abnormal but not deemed clinically significant by treating physician, approval may be given by	***Ensuring ease of recruitment while preserving safety*.**

		principal investigator upon discussion."	
Section 5.0 Study procedures table Footnote 23 Footnote 25	Stated that all day 1 labs are to be resulted before treatment.	Footnote 23: Inserted 'except ACTHand Ca19-9' , which does not need to be resulted before study drug treatment.	***For added clarity (to align with update made to section 3.1.9)***
Section 5.0 Study procedures table Footnote 25	N/A	Added test CA 19-9 to be done at baseline, D1 of each odd cycle and End of treatment visit. The test need not be resulted for treatment to begin. *(This is a standard of care test done on pancreatic cancer patients)* *Corresponding row in the table added.*	***For completeness of the list of tests that are being done on patients.***
Section 5.0 Study procedures table Footnote 1 and 14	Baseline imaging window was 14 days	Inserted langauge to indicate "Baseline imaging can be done within 21 days before registration."	***For flexibility and ease of recruitment.***
Section 5.0 Study procedures table	The visit conducted 30 days after last dose of treatment was termed as 'End of study visit'(EOS)	The term has been changed to 'end of treatment' (EOT) visit	***Correction (aimed at use of appropriate terminology)***
Section 6.7 Endpoints section (Immune-related response criteria)	Previous language regarding number of lesions to be measured for iRECIST was different from RECIST. This would lead to skewed analysis.	Language updated to make the RECIST and iRECIST sample the same targets and measured in the same dimension.	***Correction of discrepancy in order to prevent discordance.***

Amendment 2 –3.23. 2020			
Sections(s) Affected	**Prior Version**	**Amendment 2 Changes**	**Rationale**
Title page	Alfred Rademaker, PhD was listed as the statistician	Removed Alfred Rademaker, PhD Added Hui Zhang, PhD as statistician	***Alfred Rademaker has retired from NU. New statistician has been assigned for this study***
Section 4.3.1 Dose delays/modifications [for Pembrolizumab]	List of conditions/scenarios when pembrolizumab should be withheld or permanently discontinued. Included in this list are Grade 3 adverse events	Added an exception to the Grade 3 description: “ For any laboratory value that is a Grade 3 adverse event which is expected and unrelated, patient can continue to be treated I) if it is in the best interest of the patient 2) following discussion and approval of the PI”	***For flexibility.*** ***This is in response to DSMC recommendation and serves as CAPA for an RNI***
Section 4.6 Duration of therapy	Disease progression is listed as one of the criterion	Added a note: to this criterion: “ A subject may be granted an exception to continue on treatment with confirmed or unconfirmed radiographic progression , if clinically stable or clinically improved”	***For flexibility.*** ***To be consistent with Section 4.8 and to be in alignment with the objectives and endpoints of this study.***
Section 11 Study management	Previous version of template language	Updated with most current version of template language	***Administrative update***
Throughout	N/A	Minor corrections	***For consistency***