PrECOG Protocol Number: PrE0113

Oncolytics Biotech Inc. Protocol Number: REO 028

A study to assess overall response rate by inducing an inflammatory phenotype in Metastatic **BR**east c**A**n**CE**r with the Oncolytic Reovirus Pe**L**areor**E**p in Combina**T**ion with anti-PD-L**1** Avelumab and Paclitaxel –

BRACELET-1 Study

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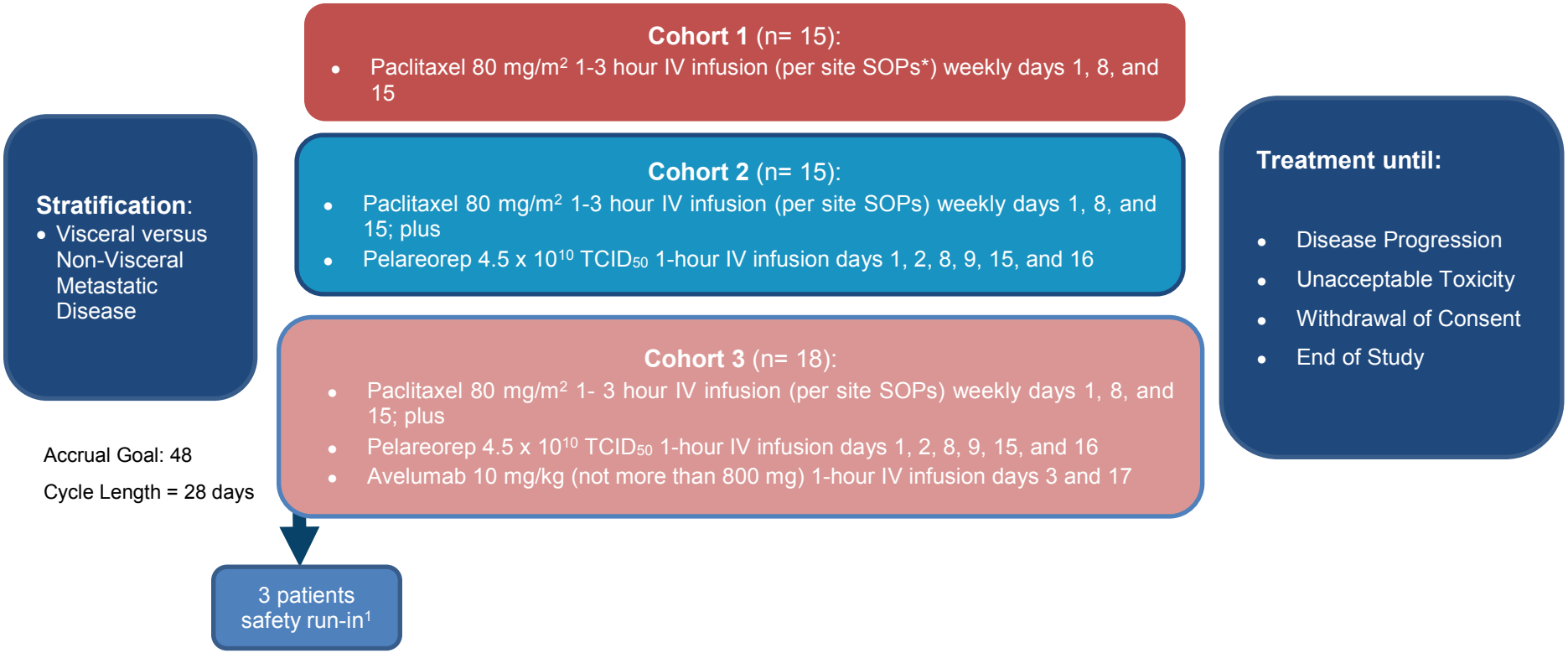
Brief Protocol Synopsis

See Protocol Document Sections for complete details

Study Schema



*SOPs = Standard Operating Procedures

1. A three patient safety run-in will be conducted in Cohort 3 prior to beginning randomization to all three cohorts. Once these patients have completed one cycle of treatment or discontinued study treatment in the event of toxicity, a safety review of the combination will be conducted. Following the safety run-in, eligible patients will be randomized 1: 1: 1.Safety run-in complete 9/21/2020. 10/22/2020: Randomized part of the study opened to enrollment following Steering Committee review of the first cycle safety data. No modifications to the protocol were made.

List of Abbreviations

5-FU	5-Fluorouracil
ACTH	Adrenocorticotropic Hormone
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
APC	Antigen Presenting Cell
ASCO-CAP	American Society of Clinical Oncology – College of American Pathologists
AST	Aspartate Transaminase
BNP	B-Type Natriuretic Peptide
BSC	Biological Safety Cabinet
BUN	Blood Urea Nitrogen
C	Celsius
CA 15-3	Carcinoma Antigen 15-3
CBC	Complete Blood Count
CBPF	Central Biorepository Pathology Facility
CCTG	Canadian Cancer Trials Group
CDK	Cyclin-Dependent Kinase
cfDNA	Cell Free DNA
CFR	Code of Federal Regulations
CI	Confidence Interval
CIVI	Continuous IV Infusion
CK	Creatine Kinase
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus Disease
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy and Evaluation Program
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
dsRNA	Double-Stranded RNA
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

eDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
EOS	End of Study
ER	Estrogen Receptor
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin Embedded
FSH	Follicle-Stimulating Hormone
G	Grams
GCP	Good Clinical Practice
GH	Growth Hormone
GITR	Glucocorticoid-Induced Tumor Necrosis Factor Receptor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER	Human Epidermal Growth Factor Receptor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HR+	Hormone Receptor+
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH GCP	International Council for Harmonisation-Good Clinical Practice
IEC	Independent Ethics Committee
IGF-1	Insulin-Like Growth Factor 1
IND	Investigational New Drug
INR	International Normalized Ratio
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
ITT	Intent To Treat
iTU	Intratumoral(ly)
IV	Intravenous(ly)
kg	Kilogram
L	Liters
LDH	Lactate Dehydrogenase
LH	Luteinizing Hormone
LV	Leucovorin
m^2	Square Meter

mBC	Metastatic Breast Cancer
MDSC	Myeloid Derived Suppressor Cells
mg	Milligrams
MHC	Major Histocompatibility Complex
mL	Milliliter
MOA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
n	Number
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCIC CTG	National Cancer Institute of Canada Clinical Trials Group
NSAID	Nonsteroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PPM	Parts Per Million
PR	Partial Response
PRL	Prolactin
PTT	Partial Thromboplastin Time
PTX	Paclitaxel
RCF	Relative Centrifugal Force
RECIST	Response Evaluation Criteria in Solid Tumors
Reovirus	Respiratory Enteric Orphan Virus
RNA	Ribonucleic Acid
RSI	Reference Safety Information
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care

SOP	Standard Operating Procedure
SRS	Stereotactic Radiosurgery
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCID	Median Tissue Culture Infective Dose
$TCID_{50}$	50% Tissue Culture Infective Dose
TEAE	Treatment-Emergent Adverse Events
TME	Tumor Microenvironment
TNBC	Triple-Negative Breast Cancer
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
vs	Versus
WBC	White Blood Count
WBXRT	Whole-Brain Radiation Therapy
WOCBP	Women of Child Bearing Potential
XRT	Radiation Therapy

1. Introduction- Background and Rationale

1.1 Breast Cancer – Disease Overview

In women worldwide, breast cancer is the most common cancer and the leading cause of cancer mortality, with approximately 1.7 million new cases diagnosed each year and over half a million deaths per year (International Agency for Research on Cancer, 2012; Torre et al., 2015). In 2015, there were an estimated 560,000 deaths due to breast cancer globally (World Health Organization, Projections of mortality and causes of death 2015 and 2030, updated July 2013), and in the United States alone in 2016, 246,660 new cases of breast cancer were estimated as well as 40,450 deaths due to metastatic disease (Siegel et al., 2016).

Despite major advances in cancer treatment over the last decades, metastatic breast cancer (mBC) remains incurable, with a median overall survival (OS) of approximately 2-3 years and a 5-year survival of only 25% (National Cancer Institute, 2014; Sundquist et al., 2017). Up to 30% of women originally diagnosed with early breast cancer will eventually progress to mBC (Berman et al., 2013; Brockton et al., 2015; Herrinton et al., 2005; O'Shaughnessy, 2005).

The current treatment for mBC is palliative with the goals to manage or prevent symptoms, control disease progression and improve quality of life (Smith, 2006). Treatment options and protocols are varied and dependent upon tumor phenotypes and genotypes.

1.2 Reovirus

Reovirus is a ubiquitous virus found in untreated sewage, stagnant water, and rivers. As such, exposure to reovirus is common, with seropositivity displayed in nearly 100% of healthy human adults (Minuk et al., 1985; Minuk et al., 1987).

The name “reovirus” was originally coined by Sabin in 1959 to reflect the fact that these viruses are typically derived from the respiratory and gastrointestinal tracts and are not associated with any known disease state, hence, they were described as “orphan” viruses. The term is an acronym for Respiratory Enteric Orphan virus (Sabin, 1959). The general structure of the reovirus particle is that of a non-enveloped virus: a double-shelled capsid, each with icosahedral symmetry, that contains 10 linear double-stranded ribonucleic acid (dsRNA) genome segments (Tyler and Fields, 1990). There are three distinct serotypes based upon antibody neutralisation and hemagglutination inhibition tests (Rosen et al., 1960).

Reovirus infections are mild and usually restricted to the respiratory and gastrointestinal tract, but on occasion, they cause flu-like upper respiratory tract symptoms and/or mild diarrhea (Jackson et al., 1963; Jackson, 1961; Jarudi et al., 1973; Lerner et al., 1962; Rosen et al., 1963; Rosen et al., 1960).

1.3 Pelareorep

Pelareorep is a propriety formulation of a naturally occurring, non-genetically modified, non-enveloped human Reovirus Serotype 3-Dearing Strain which contains live, replication-competent virus. Pelareorep has demonstrated in vitro and in vivo activity in many cancers including breast cancer and has been delivered intratumorally and intravenously. Pelareorep’s anti-tumor activity is based on a dual mechanism of action, which is complementary, but not interdependent:

- Direct oncolytic activity of tumor cells permissive to viral replication.
- Induction of anti-tumor immunity through:
    - Activation of innate immunity against virally infected tumor cells and upregulation of inflammatory cytokines.

- Increased presentation of tumor and viral-associated epitopes by antigen-presenting cells (APCs, e.g., dendritic cells), allowing for the generation of an adaptive antitumor immune response.

Thus, in addition to functioning as an oncolytic agent, pelareorep overrides the absence of anti-tumor immunity present in cancer patients, activating innate and adaptive anti-tumor immune responses. Refer to the Investigator's Brochure for a comprehensive list of references relevant to pelareorep's mechanism of action (MOA).

1.3.1 Pre-Clinical Experience with Pelareorep

In breast cancer, Norman et al. (2002) demonstrated efficient lysis of breast tumor-derived cell lines by reovirus (pelareorep strain), whereas normal breast cells are resistant to infection in vitro. In vivo studies have revealed that pelareorep can induce the regression of human breast cancer and targets breast cancer stem cells in immunocompromised mice models (Marcato et al., 2009). In immunocompetent mouse models, pelareorep as a single agent has been shown to reduce tumor burden, enhance survival, and promote protective immunity against tumor re-challenge. These anti-tumor activities are further enhanced by anti-PD-L1 combination therapy (Mostafa et al., 2018).

Pelareorep combination therapy has been shown to be synergistic with a variety of standard chemotherapeutic agents, such as taxanes (Heinemann et al., 2011; Sei et al., 2009). When used with taxanes, pelareorep is synergistic even in cells with a high level of drug resistance or limited sensitivity to the virus. Moreover, virus production or titer is increased in the presence of taxanes as viral replication complexes or inclusion bodies with cells grow in association with stabilized microtubules (Sei et al., 2009). Additionally, paclitaxel has immunomodulatory activities that may synergize with pelareorep, such as: inhibition of myeloid derived suppressor cells (MDSCs), upregulation of Programmed Death-Ligand 1 (PD-L1) and Major Histocompatibility Complex 1 (MHC1) molecules and increases in antigen presentation (Champiat et al., 2014).

1.4 Pelareorep – Clinical Experience

As of 2019, over 1400 patients have been enrolled in clinical studies of pelareorep conducted in a variety of solid tumor and hematologic cancers in the United States (US), Canada, and European Union (EU). Of these, 1065 patients received pelareorep, 974 via intravenous (IV) administration and 91 by intratumoral injections (ITu). The remaining patients were randomized to control arms and received treatment (357) or were not treated.

Pelareorep has been administered as single or multiple doses ITu or IV, either as a monotherapy or in combination with chemotherapy, immunotherapy (e.g., checkpoint inhibitors), and radiotherapy.

No Maximum Tolerated Dose (MTD) for intravenous pelareorep as monotherapy was defined in two Phase 1 trials (REO 004 and 005). When combined with chemotherapeutic agents, according to standard of care, pelareorep does not appear to enhance either the frequency or severity of the adverse effects with the exception of transient, mainly grade 1/ 2 "flu-like syndrome" after pelareorep administration, including fatigue, chills, fever, nausea and diarrhea. Doses up to 9×10^{10} $TCID_{50}$ have been well tolerated with similar safety profile.

A randomized, controlled phase 2 study (Canadian Cancer Trials Group (CCTG) IND.213) in mBC compared pelareorep plus paclitaxel versus paclitaxel alone. Following a safety run-in of 7 patients, 74 women with previously treated mBC were randomized to either treatment arm. Prior to enrolment, these patients had received at least one chemotherapy regimen for advanced/metastatic breast cancer unless they had relapsed within 6 months of completion of adjuvant chemotherapy or had received taxane and/or anthracycline

containing adjuvant chemotherapy. In this study, although no difference was seen in Progression-Free Survival (PFS) its primary endpoint of the Intent to Treat (ITT) patient population, it was found that in the test arm (pelareorep plus paclitaxel, n=36) the median OS (secondary endpoint) was 17.4 months vs. 10.4 months in the control arm (paclitaxel alone; number (n)=38; Hazard Ration (HR) 0.65; 80% Confidence Interval (CI) 0.46–0.91; p=0.1). In a post-hoc analysis in Estrogen Receptor+ (ER+) patients (n=57), the OS improved from 10.8 months on control arm to 21 months on the test arm [Cox model HR=0.60; p=0.1]. Similarly, in ER+/Progesterone Receptor + (PgR+) patients (n=47), the OS improved from 10.8 months on the control arm to 21.8 months on the test arm [Cox model HR=0.36; p=0.003] (Gutierrez et al., 2017). There were only 15 patients who were hormone receptor-negative across the groups (triple negative) and only one with HER2-positive breast cancer in the control group, so the survival analysis in these groups was inconclusive.

However, despite the small sample size, the OS results in particular in the taxane treatment naïve Hormone Receptor+ (HR+) patients are encouraging. The late benefit may explain an immune response for pelareorep and is one of the key rationales to study the combination with checkpoint inhibitor.

Of note, with the exception of a trend indicating a higher incidence of Grade ≥ 3 fatigue and a statistically significant lower incidence of Grade ≥ 3 LDH in the pelareorep plus paclitaxel combination arm, Grade ≥ 3 toxicities observed with paclitaxel were similar with or without pelareorep in this study.

1.4.1 Clinical Experience with Pelareorep in Combination with Immune Checkpoint Inhibitors

A Phase 1b study enrolled patients with metastatic adenocarcinoma of the pancreas who progressed after first line treatment. Eleven patients were treated on a 21-day cycle with 1 of 3 chemotherapy backbone regimens based on physician preference: (i) gemcitabine 1000 mg/m^2 IV on day 1, (ii) irinotecan 125 mg/m^2 IV on day 1, or (iii) leucovorin (LV) 200 mg/m^2 and 5-Fluorouracil (5-FU) 200 mg/m^2 IV bolus on day 1, followed by 5-FU 1200 mg/m^2 continuous IV infusion (CIVI) over 22 hours on day 1. Pelareorep was administered at 4.5 x 10^{10} $TCID_{50}$ (50% *tissue culture infective dose)* IV on days 1 and 2 after chemotherapy infusion. Pembrolizumab was administered at 2 mg/kg IV on day 8 (dosing based on the package insert at the time of the study design). Treatment was well tolerated with manageable toxicities. The most common grade 1 or 2 treatment-emergent adverse events (TEAEs) included fever (73%), headache (55%), chills (46%), dehydration (36%), fatigue (27%), abdominal pain (27%), vomiting (27%) and neutropenia (27%). Most events were brief and/or resolved with symptomatic treatment. One patient (gemcitabine arm) experienced transient grade 2 increased transaminases on two occasions. Grade 3 or 4 TEAEs were reported in 8 patients (45.5%), with one occurrence each of the following: abdominal pain, anemia, arthralgias, biliary obstruction, chills, deep vein thrombosis, diarrhea, fever, hyperglycemia, leukopenia, myalgias, nausea, neutropenia, pulmonary emboli, urinary tract infection, and vomiting. Disease control was achieved in 3 of 11 patients. One patient achieved partial response for 17.4 months. Two additional patients achieved stable disease, lasting 9 and 4 months, respectively. Tumor analysis from patients showed reovirus protein replication, T cell infiltration and upregulation of PD-L1.

1.5 Avelumab

Avelumab is a programmed death ligand-1 (PD-L1) blocking antibody. In the United States, avelumab is approved for the treatment of Merkel cell carcinoma, metastatic urothelial carcinoma, and advanced renal cell carcinoma in combination with axitinib. Avelumab has

been studied as a therapeutic agent in mBC in a Phase 1 trial (JAVELIN Solid Tumor; NCT01772004) (Dirix et al., 2018). Patients with mBC refractory to or progressing after standard of care therapy received avelumab IV 10 mg/kg every 2 weeks. A total of 168 patients with mBC, including 58 patients with triple-negative breast cancer (TNBC), were treated with avelumab for 2–50 weeks and followed for 6–15 months. Patients were heavily pretreated with a median of three prior therapies for metastatic or locally advanced disease. Avelumab showed an acceptable safety profile and clinical activity in a subset of patients with mBC. The overall response rate (ORR) was 3.0% overall (one complete response and four partial responses) and 5.2% in patients with TNBC. A trend toward a higher ORR was seen in patients with PD-L1+ versus PD-L1− tumor-associated immune cells in the overall population (16.7% vs. 1.6% and 22.2% vs. 2.6% in the TNBC subgroup).

In the avelumab mBC study (Dirix et al., 2018), treatment-related adverse events (AEs) of any grade occurred in 115 of 168 patients (68.5%), including a Grade ≥ 3 event in 23 patients (13.7%). The most commonly occurring treatment-related AEs of any Grade (>10% of patients) were fatigue (19.0%), infusion-related reaction (14.3%), and nausea (13.1%). Treatment-related AEs of any grade classified as immune-related occurred in 17 patients (10.1%) and include: hypothyroidism (4.8%), autoimmune hepatitis and pneumonitis (1.8% each), thrombocytopenia (1.2%), and antinuclear antibody production, dry eye, elevated rheumatoid factor, hyperthyroidism, and pemphigoid skin reaction (0.6% each). Four patients (2.4%) had a Grade ≥ 3 immune-related, treatment-related AE, including three patients (1.8%) with Grade 3 autoimmune hepatitis and one patient each with Grade 3 pneumonitis and Grade 4 thrombocytopenia (0.6% each).

1.6 Paclitaxel

Taxanes are anti-microtubule agents with significant activity in breast cancer and are part of standard of care in breast cancer when chemotherapy is indicated. Treatment guidelines on the use of paclitaxel and other chemotherapy agents for mBC vary from institution to institution across the world. Herein is a summary of current guidelines (Cardoso et al., 2017; National Comprehensive Cancer Network (NCCN) Guidelines, 2017). The weekly paclitaxel treatment used is in line with these guidelines and commonly used for the target patient population for this protocol.

1.7 Summary of Rationale for Proposed Study

1.7.1 Rationale

A previous randomized Phase 2 clinical study in advanced or mBC examining pelareorep in combination with paclitaxel showed an improvement in OS from 10.4 months with paclitaxel alone to 17.4 months with pelareorep + paclitaxel (HR=0.65, 80% CI 0.46–0.91, p=0.1). In a post hoc subgroup analysis, the median OS improved from 10.8 months with paclitaxel alone to 21.0 months with pelareorep + paclitaxel (p=0.1; Cox model HR=0.60; n=57) in ER+ patients. However, in the ITT population, pelareorep + paclitaxel did not improve PFS or overall response rate relative to paclitaxel alone, suggesting a late onset immune response.

A study with avelumab in patients with mBC achieved an overall response rate of 3% in the ITT population, however patients with PD-L1 positive tumor-associated immune cells achieved a higher ORR (16.7%) compared to patients with PD-L1 negative tumor-associated immune cells (1.6%) (Dirix et al., 2018). A similar study in advanced TNBC found that in patients treated with atezolizumab and Nab-paclitaxel, the ORR is greater in PD-L1 positive tumors (41.4%) relative to PD-L1 negative tumors (33.3%) (Adams et al., 2018).

Thus, pelareorep mediated immunological responses that upregulate PD-L1 expression and prime the tumor microenvironment (TME) for treatment with

checkpoint blockade may allow for enhanced objective responses when avelumab is added to pelareorep + paclitaxel. Both clinical and preclinical studies have demonstrated that pelareorep can promote an inflamed TME, increasing the number of tumor infiltrating lymphocytes and enhancing the expression of PD-1/PD-L1 within tumors. Thus, we hypothesize that the addition of anti-PD-L1 therapy to pelareorep and paclitaxel in patients with mBC will be synergistic and improve efficacy in terms of ORR compared to paclitaxel monotherapy and paclitaxel + pelareorep combination therapy.

1.7.2 Study Design

This is an open-label randomized Phase 2, 3-cohort study in Hormone Receptor+ (HR+)/Human Epidermal Growth Factor Receptor 2 negative (HER2-) with endocrine-refractory metastatic breast cancer.

Endocrine-refractory is defined as progression while on endocrine therapy and CDK4/6 inhibitor therapy. Prior treatment with an mTOR inhibitor is allowed but is not required. Patients may have received several lines of anti-hormone therapies but should not have received chemotherapy for metastatic disease.

Patients may have received chemotherapy in the (neo)adjuvant setting. Patients receiving (neo)adjuvant taxanes must have a disease-free interval of at least 12 months.

Patients will continue to receive study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or End of Study (EOS). Any patients who remain on study treatment when EOS is reached will be eligible to continue that treatment through an expanded access protocol.

Patients who discontinue study treatment will continue to be followed for survival until they have withdrawn consent, been lost to follow-up, died, or EOS is reached, whichever occurs first.

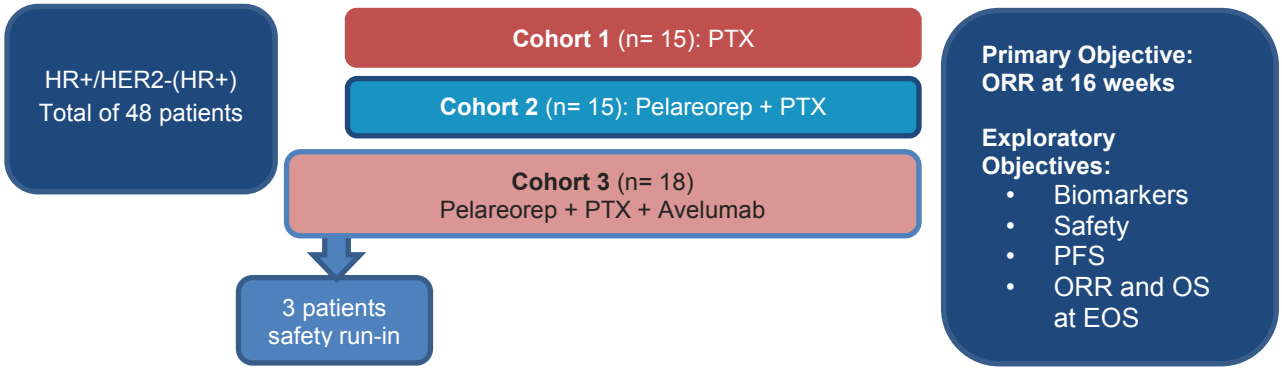
End of Study will occur when all patients have reached at least 2 years of study participation (measured from the first day of study treatment; including treatment and follow up), withdrawn consent, been lost to follow up, or died.

Reduced clinical data will be collected in study treatment cycles past week 16, per Section 10. Blood samples for biomarker analyses will be collected on Day 1 of every cycle of study treatment.

Cohort 1: Control group with dosing of weekly paclitaxel (PTX) according to standard of care (SOC)

Cohort 2: Investigative treatment with pelareorep added to SOC (PTX)

Cohort 3: Investigative treatment with pelareorep in combination with avelumab added to SOC (PTX)



1.7.3 Safety Phase

A three patient safety run-in will be conducted in Cohort 3 (pelareorep+avelumab+ paclitaxel) prior to beginning randomization into all three cohorts. A safety evaluation will be conducted after all 3 patients have completed one 28 day cycle of treatment (i.e., received all the doses for all the drugs per protocol) or discontinued the therapy before completion of Cycle 1 due to toxicity (i.e., permanently discontinued or dose held). Patients who discontinue the therapy before completion of Cycle 1 due to reasons other than toxicity will be replaced.

During the safety review, a Steering Committee will review all the safety data captured during the first cycle of treatment and make recommendations to continue, alter, or permanently suspend the study based on this analysis. The Steering Committee may recommend amendments to explore alternate dosing schedules or lower doses based on the overall toxicity experience, even if the criteria for dose-limiting toxicity (DLT) are not met (Section 5.2).

During this review period, enrolled patients may continue to receive study treatment.

1.7.3.1 Safety Run-In Complete

9/21/2020: Safety run-in completed.

10/22/2020: Randomized part of the study opened to enrollment following Steering Committee review of the first cycle safety data. No modifications to the protocol were made.

1.7.4 Patient randomization and stratification factors

- Patients will be stratified for visceral versus non-visceral metastatic disease
- Patients will be randomized as 1:1:1 (PTX vs. PTX + pelareorep vs. PTX + pelareorep + avelumab).

1.7.5 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, eligibility criteria not met or rationale for not enrolling despite meeting all eligibility criteria, and any serious adverse events

(SAEs) that occurred due to screening procedures required for the study. This information can be maintained in a Screen Failures Log at the study site.

2. Study Objectives

This is an exploratory Phase 2 study to inform the design of a subsequent registration study.

2.1 Primary Objective

- Determine the efficacy in terms of overall response rate (ORR) at week 16 according to RECIST V1.1

2.2 Other Objectives (these objectives are all exploratory)

- Examine efficacy in terms of OS and ORR at EOS according to RECIST V1.1.
- Examine efficacy in terms of PFS.
- Examine the safety of the combination:
  - To be assessed using serious and non-serious adverse events (clinical and laboratory), laboratory parameters, treatment exposure (total delivered dose and dose modifications) and reasons for treatment discontinuation.
- Examine biomarkers to determine the immunological changes within the TME and peripheral blood in patients treated with paclitaxel alone, in combination with pelareorep, and in combination with pelareorep and avelumab.

  Key assays will:
  - Examine the expression of immune-related biomarkers, such as PD-1 and PD-L1.
  - Identify biological changes, as defined by changes in gene expression within the TME and Peripheral Blood Mononuclear Cells (PBMCs), between pre-treatment and on-therapy specimens.
  - Compare changes in the T cell repertoire between pre-treatment and on-therapy tumor biopsies; examining common T cell clones between tumor tissue and peripheral blood samples.
  - Compare changes in the T cell repertoire between pre-treatment and on-therapy peripheral blood samples.
  - Examine tumor mutational burden and prevalent Deoxyribonucleic Acid (DNA) mutations in all patients from Cell Free Deoxyribonucleic Acid (cfDNA).

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

PrECOG Patient No. _____

Patient's Initials (F, M, L) _____

Physician Signature and Date _____

NOTE: PrECOG does not allow waivers to any protocol specified criteria. Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and a major protocol violation. All questions regarding clarification of eligibility criteria must be directed to PrECOG Study Contact.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

Inclusion Criteria

_____ 3.1 Female patients ≥ 18 years of age at the time of signing the informed consent form (ICF).

_____ 3.2 Must have a histological/cytological diagnosis of breast cancer. Disease must be:

- Positive for estrogen receptor (ER) and/or progesterone receptor (PgR) as defined by ≥ 1% tumor cell nuclei immunoreactive.
- Negative for HER2 amplification / overexpression as defined per the American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines. However, patients with HER2 equivocal disease for whom HER2 targeted therapy isn't indicated are also eligible for enrollment.

Date of Initial Diagnosis: _____

_____ 3.3 ECOG performance status of 0-1 (Appendix I).

_____ 3.4 Must have unresectable locally advanced or metastatic disease, for which no curative therapy exists and for which systemic chemotherapy is indicated.

_____ 3.5 Measurable disease as defined by RECIST Version 1.1 (Appendix II).

_____ 3.6 Prior Hormonal Therapy:

- Patients must have progressed on at least 1 hormone-based therapy with a CDK4/6 inhibitor. Patients who received a CDK4/6 inhibitor in the adjuvant setting and progressed while on or within 6 months of discontinuation of CDK4/6 inhibitor therapy are eligible.
- Prior mTOR inhibitor therapy is allowed but is not required.

Date of Last Therapy: _____

_____ 3.7 Ability to understand and willingness to sign IRB-approved informed consent.

_____ 3.8 Willing to provide blood samples for research (Section 13.0).

_____ 3.9 Adequate organ function as measured by the following criteria, obtained ≤ 2 weeks prior to registration:

Hematology:

Neutrophils	≥ 1.5 x 10^9/L	Neutrophils: _____	Date of Test: _____
Platelets	≥ 100 x 10^9/L	Platelets: _____	Date of Test: _____
Lymphocytes	≥ 0.8 x 10^9/L	Lymphocytes: _____	Date of Test: _____
INR	≤ 1.5x ULN	INR: _____ (Unless on therapeutic anticoagulation)	Date of Test: _____
PTT	≤ 1.5x ULN	PTT: _____	Date of Test: _____

Biochemistry:

Serum Creatinine

≤ 1.5x ULN	Serum Creatine: _____	Date of Test: _____

Total Bilirubin ≤ 1.0x ULN *(unless due to Gilbert's Disease and direct bilirubin <ULN)*

Total Bilirubin: _____	ULN: _____	Date of Test: _____

ALT and AST ≤ 3x ULN (Note: ≤ 5x ULN if documented liver metastasis)

ALT: _____	ULN: _____	Date of Test: _____
AST: _____	ULN: _____	Date of Test: _____

Proteinuria ≤ Grade 2* (using spot testing; if Grade 3 repeat with mid-stream urine; if still Grade 3 then urine collection for 24 hours to confirm Grade 0, 1 or 2)
*as per National Cancer Institute Common Terminology Criteria for Adverse (NCI-CTCAE)

Proteinuria: _____	Grade: _____	Date of Test: _____

_____ 3.10 Women must not be pregnant or breastfeeding since we do not know the effects of the study drugs on the fetus or breastfeeding child. All sexually active females of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a blood test to rule out pregnancy within 2 weeks prior to registration.

Is the patient a woman of childbearing potential? _____ (yes/no)

If yes, Date of Test: _____ Results: _____

_____ 3.11 Sexually active women of child-bearing potential with a non-sterilized male partner must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation, and for 3 months following last dose of study drugs. Method of contraception must be documented.

NOTE: If a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Exclusion Criteria

_____3.12 No major surgery within 21 days prior to beginning study treatment. Major surgery >21 days prior to beginning study treatment is permitted provided that the patient has recovered adequately to receive systemic chemotherapy. **NOTE**: Placement of a vascular access device is not considered major surgery.

_____ 3.13 Patients who have received radiation treatment within 14 days of beginning study treatment are excluded. Patients who have received palliative radiation ≥ 14 days prior to beginning study treatment may enroll if they have recovered from all local and systemic side effects to ≤ Grade 1 (NCI-CTCAE).

_____ 3.14 No prior chemotherapy in the advanced/metastatic setting is allowed. Patients may have received chemotherapy in the (neo)adjuvant setting. Patients receiving (neo)adjuvant taxanes must have a disease-free interval of at least 12 months.

_____ 3.15 No known active, uncontrolled or symptomatic Central Nervous System (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with CNS metastases treated with radiation therapy (Whole-Brain Radiation Therapy [WBXRT] or Stereotactic Radiotherapy [SRS]) are eligible if, >28 days following completion of XRT, they show stable disease on post-treatment MRI/CT, are off corticosteroids, and are neurologically stable.

_____ 3.16 No known history of other malignancies, except for adequately treated non-melanoma skin cancer or solid tumors curatively treated with no evidence of disease for >3 years.

_____ 3.17 Not on chronic immunosuppressive therapy including, but not exclusively, steroids (≥ 10 mg prednisone a day or equivalent) or monoclonal antibodies, chronic methotrexate or cyclophosphamide, tacrolimus or sirolimus.

_____ 3.18 No known HIV infection. Testing not required in absence of clinical suspicion.

_____ 3.19 No known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection or undergoing anti-viral treatment. Testing for HBV/HCV is not required in absence of clinical suspicion.

_____ 3.20 No concurrent disease or condition that would interfere with study participation or safety, such as any of the following:

- Active, clinically significant infection either Grade >2 by CTCAE V5.0 or requiring the use of parenteral anti-microbial agents within 14 days before registration.

_____ 3.21 No active or history of any autoimmune disease (patients with diabetes Type 1, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible) or immunodeficiencies.

_____ 3.22 Patients may not have evidence of uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure (New York Heart Association [NYHA] Class III or higher [Appendix III]), unstable angina, or myocardial infarction within the past 6 months prior to registration. **NOTE:** Patients with asymptomatic rate-controlled atrial fibrillation may participate.

_____ 3.23 Patients may not have other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the patient's tolerance of trial treatment.

_____ 3.24 Patients with a known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent are not eligible.

_____ 3.25 Patients who have contraindications to treatment with paclitaxel and/or neuropathy >Grade 2 are not eligible.

_____ 3.26 Patients who have not recovered from clinically significant acute toxicities of previous therapy are not eligible, except treatment-related alopecia or stable sensory neuropathy ≤ Grade 2.

_____ 3.27 No prior therapy with any investigational anti-cancer therapy within 30 days. Prior immunotherapies are prohibited (see 3.28).

_____ 3.28 No prior therapy with checkpoint inhibitors (e.g., anti-PD-1/PD-L1 antibodies), checkpoint agonist agents (e.g., anti-GITR, anti-OX40 antibodies) and/or another active immunotherapy in breast cancer such as cancer vaccines or oncolytic virsus.

_____ 3.29 Patients with any serious medical or psychiatric illness that could, in the Investigator's opinion, potentially interfere with the completion of the treatment according to the protocol, are not eligible.

_____ 3.30 Patients with legal incapacity or limited legal capacity are not eligible.

_____ 3.31 Patients with known alcohol or drug abuse are not eligible.

_____ 3.32 Patients may not participate in any other therapeutic clinical trials, including those with other investigational agents not included in this trial, throughout the duration of this study.

_____ 3.33 Patients may not have any vaccine, including against SARS-COV-2 (COVID-19) <14 days prior to C1D1 nor in the first cycle of study treatment. Inactivated vaccines (including against COVID-19 or seasonal influenza) are permitted after the first cycle of study treatment is complete.

4. Registration Procedures

4.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with applicable US regulatory requirements and International Conference on Harmonization/Good Clinical Practice (ICH/GCP).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Freely given written informed consent must be obtained from every patient or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish patient eligibility for the trial.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of Investigators or study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Investigators are responsible for the conduct of the study at their study site.

4.2 Regulatory Requirements

Before a site may enroll patients, protocol-specific regulatory and other documents must be submitted to PrECOG as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Once required documents are received, reviewed, and approved by PrECOG or their representative, study materials will be forwarded to the site. Any changes to site regulatory documents must be submitted by the Investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. Once PrECOG activates a site, enrollment may occur. No patients will begin protocol therapy without formal registration as per the process below.

4.3 Patient Registration

Patients must not start protocol treatment prior to registration.

Patients must meet all of the eligibility requirements listed in Section 3 prior to registration. Treatment should begin ≤ 10 working days from date of registration.

An eligibility checklist is included in Section 3. A confirmation of eligibility assessment by the Investigator and/or site will be performed during the registration process.

A three patient safety run-in will be conducted in Cohort 3 prior to beginning randomization to all three cohorts. The first 3 patients enrolled will be registered into the study after confirmation of eligibility.

Once these patients have completed one cycle of treatment or have discontinued study treatment in the event of toxicity, a safety review of the combination will be conducted. If the study continues after the safety review, all remaining patients will require randomization into Cohort 1 or Cohort 2 or Cohort 3.

After it is verified by the site that the patient meets all eligibility criteria, randomization will occur by entering the patient in the electronic Data Capture (eDC) system.

Confirmation of randomization/registration will be displayed in the eDC system.

Full information regarding registration procedures and guidelines can be found in the materials provided to your site. Documentation from the web randomization system

including the treatment assignment will be placed in the patient record. Correspondence regarding patient registration must be kept in the study records.

4.4 Research Tissue and Blood Samples

Time points for tissue and blood samples are outlined in the study parameters (Section 10) and specific requirements are outlined in the correlative section of this protocol (Section 13) and the lab manual.

5. Treatment Plan

5.1 Overview

This is an open-label randomized Phase 2, 3-cohort study for patients with hormone receptor (HR)-positive (HR+)/ Human Epidermal Growth Factor Receptor 2 (HER2)-negative (HER2-), endocrine-refractory metastatic breast cancer. A total of 48 patients will be enrolled and will be treated until progression, unacceptable toxicity, withdrawal of consent, or EOS. The study will be conducted at approximately 20 US-based study centers.

A three patient safety run-in will be conducted in Cohort 3 (pelareorep+avelumab+ paclitaxel) prior to beginning randomization into all three cohorts.

Following the safety run-in, eligible patients will be randomized 1: 1: 1. Each cohort will enroll 15 patients.

Cohort 1: Paclitaxel (PTX)

Cohort 2: PTX + pelareorep

Cohort 3: PTX + pelareorep + avelumab

Patients will be stratified for visceral versus non-visceral metastatic disease.

5.2 Cohort 3 Safety Run-In

A three patient safety run-in will be conducted in Cohort 3 (pelareorep+avelumab+ paclitaxel) prior to beginning randomization into all three cohorts. A safety evaluation will be conducted after all 3 patients have completed one cycle of treatment (i.e., received all the doses for all the drugs per protocol) or discontinued the therapy before completion of Cycle 1 due to toxicity (i.e., permanently discontinued or dose held). Patients who discontinue the therapy before completion of Cycle 1 due to reasons other than toxicity will be replaced.

During the safety review, a Steering Committee will review all the safety data captured during the first cycle of treatment and make recommendations to continue, alter, or permanently suspend the study based on this analysis. The Steering Committee may recommend amendments to explore alternate dosing schedules or lower doses based on the overall toxicity experience, even if the criteria for dose-limiting toxicity (DLT) are not met. Events that occur after completion of the first cycle of study treatment will not be included in the safety review or evaluated as potential DLTs.

During this review period, enrolled patients may continue to receive study treatment.

5.2.1 Dose-Limiting Toxicity (DLT) Evaluation for Safety Run-In

Table 5-1: DLT Evaluation for Safety Run-In

Toxicity Category	Criteria Defining a DLT
Hematological	Grade 4 neutropenia lasting ≥ 7 days
	Febrile Neutropenia (any grade)

	Grade 4 thrombocytopenia lasting ≥ 7 days **OR** Grade 3 thrombocytopenia associated with clinically significant bleeding
Non-Hematological	Grade ≥ 3 nausea and/or vomiting that persists for at least 72 hours and is unresponsive to adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the Investigator.
	Other Grade ≥ 3 toxicity that persists for ≥ 7 days or recurs despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the Investigator.
	If baseline AST and ALT <2.5x ULN: DLT will be ALT or AST >5x ULN If baseline AST and ALT ≥ 2.5x ULN: DLT will be ALT or AST >8x ULN
Any toxicity that results in a >14 day delay in treatment will be considered a DLT.	
Any death not clearly due to underlying disease or extraneous causes will be considered a DLT.	

5.3 Treatment and Administration Schedule

Following the safety run-in, eligible patients will be randomized 1: 1: 1. Each cohort will enroll 15 patients.

Patients from each cohort will receive the following treatment during a 28-day cycle:

Cohort 1:

- Paclitaxel 80 mg/m^2 1-3 hour IV infusion (per site SOPs) weekly days 1, 8, and 15.

Cohort 1

	Week 1							Week 2							Week 3							Week 4							REPEAT
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Paclitaxel	X							X							X														

Cohort 2:

- Paclitaxel 80 mg/m^2 1-3 hour IV infusion (per site SOPs) weekly days 1, 8, and 15; plus
- Pelareorep 4.5 x 10^{10} $TCID_{50}$ 1-hour IV infusion days 1, 2, 8, 9, and 15, 16.

On days that require treatment with both pelareorep and paclitaxel, pelareorep must be given at least 30 minutes after the completion of the paclitaxel infusion.

Patients in Cohort 2 who discontinue paclitaxel for toxicity can continue with pelareorep monotherapy if, in the Investigator's opinion, they may be experiencing therapeutic benefit, their disease has not progressed, and written approval has been obtained from PrECOG.

Cohort 2

	Week 1							Week 2							Week 3							Week 4							REPEAT
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Pelareorep	X	X						X	X						X	X													
Paclitaxel	X							X							X														

Cohort 3:

- Paclitaxel 80 mg/m^2 1-3 hour IV infusion (per site SOPs) weekly days 1, 8, and 15; plus
- Pelareorep 4.5 x 10^{10} $TCID_{50}$ 1-hour IV infusion days 1, 2, 8, 9, and 15, 16.
- Avelumab 10 mg/kg (not more than 800 mg) 1-hour IV infusion days 3 and 17.

On days that require treatment with both pelareorep and paclitaxel, pelareorep must be given at least 30 minutes after the completion of the paclitaxel infusion.

Patients in Cohort 3 who discontinue paclitaxel for toxicity can continue with pelareorep and/or avelumab monotherapy or combination therapy if, in the Investigator's opinion, they may be experiencing therapeutic benefit, their disease has not progressed, and written approval has been obtained from PrECOG.

Cohort 3

	Week 1							Week 2							Week 3							Week 4							REPEAT
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Pelareorep	X	X						X	X						X	X													
Paclitaxel	X							X							X														
Avelumab			X														X											

Study treatment in all cohorts will continue until disease progression, unacceptable toxicity, withdrawal of consent, or EOS. Cross-over between cohorts is not permitted.

5.4 Premedications

Premedication for Paclitaxel
Prophylactic dexamethasone, diphenhydramine, and ranitidine prior to each paclitaxel infusion. The suggested premedication regimen is: dexamethasone 10 mg IV, diphenhydramine 50 mg IV, and ranitidine 50 mg IV all given 30 minutes before paclitaxel infusion. Adjustments to this suggested premedication regimen to be consistent with local standards is allowed.

Premedication for Avelumab
Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions (see Warnings and Precautions of Avelumab Investigator's Brochure). Refer to Premedication for Pelareorep, below, for maximum daily permitted dose of acetaminophen.

Premedication for Pelareorep
Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) may be used for the prophylaxis or treatment of the flu-like signs and symptoms, especially fever, that are commonly associated with pelareorep. Guidelines for the use of acetaminophen and NSAIDs are as follows:

Acetaminophen:

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

NSAIDs:

- The decision to use oral NSAID should be made for each individual patient, with attention to the patient's renal and hydration status at the time of pelareorep administration or the time of imaging scans with contrast.
- Dose should not exceed ibuprofen 800 mg or equivalent per dose (ibuprofen 3200 mg/day or equivalent).

6. Dose Modifications and Discontinuation of Therapy

6.1 Dose Delays & Modifications

All toxicities should be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE V5.0). A copy of the CTCAE V5.0 can be downloaded from the CTEP website (http://www.ctep.cancer.gov).

A +/-2 day window is allowed for scheduled therapy, required tests and/or visits except as otherwise noted. If the first day of paclitaxel/pelareorep treatment is delayed (in Cohorts 2 and 3), the following day of treatment must also be delayed, as two pelareorep doses cannot be delivered on the same day. For cohort 3, pelareorep and avelumab cannot be delivered on the same day. Dose delays >2 days will be considered missed and will not be replaced. Delays due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

For Cohort 3 Safety Run-In for Cycle 1 please refer to Table 5-1 for criteria for defining DLT.

NOTE: Response evaluation must be performed every 8 weeks until week 16, then every 12 weeks even if cycles are delayed. When treatment is held for >4 weeks and <8 weeks, authorization from PrECOG must be obtained before restarting therapy. If study treatment is held for 8 weeks or more, the patient will discontinue study therapy permanently.

Dose interruptions for ≤ 4 weeks for non-drug-related reasons (e.g., surgery, radiotherapy, holiday break, etc.) may be allowed after patients complete the response assessment at Week 16, and with the agreement of the Investigator and PrECOG.

Patients in Cohort 2 who discontinue paclitaxel for toxicity can continue with pelareorep monotherapy if in the Investigator's opinion, they may be experiencing therapeutic benefit, their disease has not progressed, and approval has been obtained from PrECOG. Similarly, patients in Cohort 3 who discontinue paclitaxel for toxicity can continue with pelareorep and/or avelumab monotherapy or combination therapy if in the Investigator's opinion, they may be experiencing therapeutic benefit, their disease has not progressed, and approval has been obtained from PrECOG.

NOTE: Patients who continue treatment with pelareorep alone (Cohort 2) or pelareorep and/or avelumab (Cohort 3) are considered on study and evaluations and data submission is required until study closure as outlined in Section 10.

6.1.1 Pelareorep

In the event of toxicity ≥ Grade 2 considered reasonably related to pelareorep, the Investigator may choose to hold the dose of pelareorep until the toxicity resolves to Grade 0 or 1 or baseline, per the recommendations below. Dose delays >2 days will be considered missed and will not be replaced.

Non-Hematologic Toxicity:

In the event a ≥ Grade 2 non-hematologic toxicity occurs which is considered reasonably related to pelareorep, the Investigator may choose to hold the dose of pelareorep until achieving a complete or partial resolution (Grade 0 to 1) of the toxicity, or return to baseline. Pelareorep should not be restarted until the laboratory requirements defined below have been met or have returned to baseline values:

Table 6-1: Criteria for Pelareorep Administration for Serum Creatinine, Total Bilirubin and ALT/AST	
Serum Creatinine	≤ 1.5x ULN
Total Bilirubin	≤ 1.0x ULN (unless elevated secondary to conditions such as Gilbert's Disease)
ALT and AST	≤ 3x ULN (Note: ≤ 5x ULN if documented liver metastasis)

If the non-hematologic toxicity resolves to Grade 1 or baseline within 4 weeks, patients can continue therapy at the same dose and as per the original schedule.

Table 6-2: Criteria for Pelareorep Administration for Proteinuria	
Degree of Proteinuria	**Pelareorep Dosing**
Grade 1	Administer pelareorep dose as scheduled.
Grade 2	Hold dose. Urine microscopy and collect 24-hour urine for protein - If protein <1.0 g/24 hours AND no evidence glomerulonephritis on microscopy, restart pelareorep at same dose. - If protein ≥ 1.0 g/24 hours OR active sediment (suggestive of glomerulonephritis), investigate further (nephrology consultant). May restart at scheduled dose when protein <1.0 g/24 hours AND no evidence of glomerulonephritis.
Grade 3	
Grade 4	Hold dose. Obtain urine microscopy and collect 24-hour urine for protein at noted above. May restart once toxicity resolves to ≤ Grade 1 or baseline.

Hematologic Toxicity:

Patients with Grade 1-2 neutropenia, lymphopenia or thrombocytopenia can be treated with pelareorep as scheduled. Pelareorep dose must be held for patients with Grade 3-4 neutropenia, lymphopenia or thrombocytopenia. These patients can restart therapy when values have returned to baseline or the following laboratory requirements are met:

Table 6-3: Criteria for Pelareorep Administration for Hematologic Toxicity	
Platelets	≥ 75 x 10^9/L
Neutrophils	≥ 1.0 x 10^9/L
Lymphocytes	≥ 0.8 x 10^9/L

6.1.2 Paclitaxel

Dose adjustments of paclitaxel for hematological, non-hematological, and hepatic toxicities can be made according to the study site's standard procedures. Patients should be monitored closely for the development of profound myelosuppression.

6.1.3 Avelumab

Dose modifications of avelumab for immune-related adverse reactions are provided in the table below. Refer to the avelumab IB for further information and guidance on the management of infusion related reactions.

Table 6-4: Avelumab – Management of Immune-Related Adverse Events (irAEs)
NCI CTCAE V5 (modified)*

Gastrointestinal irAEs		
Severity of Diarrhoea/Colitis	**Initial Management**	**Follow-Up Management**
Grade 1 Diarrhoea: <4 stools/day over Baseline Colitis: Asymptomatic	Continue avelumab therapy. Symptomatic treatment (e.g., loperamide).	Close monitoring for worsening symptoms. Educate subject to report worsening immediately. If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhoea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with activities of daily living (ADL) Colitis: Abdominal pain; blood in stool	Withhold avelumab therapy. Symptomatic treatment.	If improves to Grade ≤ 1: Resume avelumab therapy. If persists >5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhoea (Grade 3): ≥ 7 stools per day over Baseline; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): Severe abdominal pain, peritoneal signs Grade 4: Life-threatening consequence including perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication). **Note:** Infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash	**Initial Management**	**Follow-Up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy. Symptomatic therapy (for example, antihistamines, topical steroids).	If Grade 2 persists >1 to 2 weeks or recurs: Withhold avelumab therapy. Consider skin biopsy. Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area;	Withhold avelumab for Grade 3.	If improves to Grade ≤ 1:

Grade 4: Life-threatening consequences	Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy. Dermatology consult. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis	**Initial Management**	**Follow-Up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy. Monitor for symptoms every 2 to 3 days. Consider Pulmonary and Infectious Disease consults.	Re-assess at least every 3 weeks. If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy. Pulmonary and Infectious Disease consults. Monitor symptoms daily; consider hospitalization. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	Re-assess every 1 to 3 days. If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper. If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improves to Grade ≤ 1: Taper steroids over at least 1 month. If not improving after 48 hours or worsening: Add additional immunosuppression (for example: infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation	**Initial Management**	**Follow-Up Management**
Grade 1 Grade 1 AST or ALT >ULN to 3.0x ULN and/or total bilirubin >ULN to 1.5x ULN	Continue avelumab therapy.	Continue liver function monitoring. If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤ 5x ULN and/or total bilirubin >1.5 to ≤ 3x ULN	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists >5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5x ULN and/or total bilirubin >3x ULN	Permanently discontinue avelumab therapy. Increase frequency of monitoring to every 1 to 2 days.	If returns to Grade ≤ 1: Taper steroids over at least 1 month. If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily.

	1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consult Gastroenterologist/ Hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased	**Initial Management**	**Follow-Up Management**
Grade 1 Creatinine increased >ULN to 1.5x ULN	Continue avelumab therapy.	Continue renal function monitoring. If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤ 6x ULN	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	If returns to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased >6x ULN	Permanently discontinue avelumab therapy. Monitor creatinine daily. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephrology consult.	If returns to Grade ≤ 1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-Up Management**
New onset of cardiac signs or symptoms and/or new laboratory cardiac biomarker elevations (e.g., troponin, CK-muscle/brain, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule out immune-related myocarditis. Guideline based supportive treatment as per cardiology consult.** Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-related etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-related myocarditis.

Immune-Related Myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.** 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g., azathioprine, cyclosporine A).
**Local guidelines, or e.g. European Society of Cardiology or American Heart Association guidelines European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines American Heart Association guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-Up Management**
Grade 1 or Grade 2 Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type I diabetes mellitus)	Continue avelumab therapy. Endocrinology consult if needed. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule out secondary endocrinopathies (i.e., hypopituitarism/hypophysitis).	Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type I diabetes mellitus)	Withhold avelumab therapy. Consider hospitalization. Endocrinology consult. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule out secondary endocrinopathies (i.e., hypopituitarism/hypophysitis).	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e., subnormal serum thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone):	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/ suppression therapy as appropriate.

	- Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women). - Hormone replacement/ suppressive therapy as appropriate. - Perform pituitary MRI and visual field examination as indicated. **If hypophysitis confirmed:** - Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month. - Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. - Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of Other irAEs	**Initial Management**	**Follow-Up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation.	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy. If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent.	If improves to Grade ≤ 1: Taper steroids over at least 1 month.

	Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	
Grade 4	Permanently discontinue avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections. Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency. **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer.**	Permanently discontinue avelumab therapy. Specialty consult.	

ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; CK = creatine kinase; CT = computed tomography; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; irAE = immune-related adverse event; IV = intravenous; LH = luteinizing hormone; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PRL = prolactin; ULN = upper limit of normal.

*CTCAE definitions may have been modified for this purpose. Definitions may not be identical to the CTCAE V.5.

6.2 Concurrent Therapies

6.2.1 Required and/or Permitted

Permitted medications include, but are not limited to:

- Supportive and palliative care as required throughout the study.
- Growth factors, according to local institutional policy.
- Anti-emetics or anti-diarrheal agents as required.
- Skeletal protective therapy with bisphosphonates.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.2.2 Not Permitted

- Other anti-cancer therapy or investigational therapy.
- Chronic methotrexate, cyclophosphamide, tacrolimus or sirolimus.
- Other monoclonal antibodies.
- Vaccines <14 days prior to beginning study treatment and during Cycle 1. Inactivated vaccines (against COVID-19 or seasonal influenza, for example) are permitted after Cycle 1 is complete. Live vaccines are not permitted while on study treatment.

6.2.3 Concomitant Medications

Concomitant medications used to treat SAEs are to be recorded in the eCRF. In addition, concomitant medications used to treat any AE that, in the Investigator's opinion, is immune-related are to be recorded in the eCRF. Steroids also need to be recorded.

If participants receive an inactivated vaccine after they have completed the first cycle of study treatment (see 6.2.2), it must be entered in the eCRF.

No other concomitant medications need to be captured.

7. Study Duration and Discontinuation of Therapy

7.1 Study Duration – General Considerations

Study Treatment will continue until disease progression (per RECIST Version 1.1), unacceptable toxicity, withdrawal of consent, or EOS. Any patients who remain on study treatment when EOS is reached will be eligible to continue that treatment through an expanded access protocol.

Crossover between cohorts is not permitted.

7.2 End of Study

End of Study will occur when all patients have reached at least 2 years of study participation (measured from the first day of study treatment; including treatment and follow-up), withdrawn consent, been lost to follow up, or died.

7.3 Duration of Follow-Up

Safety Follow-Up:

Patients will be followed for adverse events for 30 days after their last dose of study medication or the initiation of non-protocol therapy after last dose of study medication, whichever comes first. However, if a patient experiences a serious adverse event >30 days after their last dose of study medication that is felt to be, in the opinion of the Investigator, possibly, probably or definitely related to study therapy, the serious adverse event should be reported.

Response Follow-Up:

Tumor response per to RECIST V1.1 will be assessed by CT scan every 8 weeks until week 16, and every 12 weeks thereafter until discontinuation of study treatment, regardless of dose interruptions or dose delays. Patients who discontinue study treatment for reasons other than progression will continue to be followed for tumor response per standard of care until progression, initiation of a new therapy, or withdrawal of consent, whichever occurs first.

Survival Follow-Up:

Patients who discontinue study treatment will continue to be followed by phone for survival status every 4-6 months. Patients will be followed until they have withdrawn consent, been lost to follow-up, died, or EOS; whichever occurs first.

Patients who are registered but do not receive any protocol therapy will not be included in any analyses and data past baseline will not be collected.

7.4 Criteria for Removal from Study Treatment

Reasons that a patient may discontinue treatment in this clinical study are listed below. The reason for discontinuation will be recorded in each patient's eCRF:

1. Recurrence of disease or documented progression of disease.
2. Intercurrent illness that prevents further administration of treatment per Investigator discretion.
3. Unacceptable adverse events.
4. Treatment interruption of ≥ 8 consecutive weeks.
5. Pregnancy.

6. Second malignancy (except for non-melanoma skin cancer or cervical carcinoma in-situ) that requires treatment, which would interfere with this study.
7. Patient withdraws consent at any time for any reason.
8. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the Investigator.
9. Severe non-compliance with protocol as judged by the Investigator.
10. Lost to follow-up.
11. Death.
12. Closure of study by PrECOG.

Any patient who receives at least one dose of study drug will be included in the safety analysis. If a patient is removed from treatment for reason(s) other than progression follow with regular tumor assessments per standard of care until progression per RECIST v 1.1, start of new treatment, or withdrawal of consent, whichever occurs first.

Note: Any patients who remain on study treatment when EOS is reached will be eligible to continue that treatment through an expanded access protocol.

8. Adverse Event Reporting

8.1 AE Definition

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

8.2 Assessment of Seriousness

A Serious Adverse Event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the patient or require intervention to prevent one of the outcomes listed.

Seriousness in relation to adverse events is not the same as severity. For example, an adverse event assessed to be severe (Grade 3) per the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 may not be serious. All adverse events noted as "serious" in the eCRF are reported as Serious Adverse Events in accordance with Section 8.9.

8.3 Assessment of Severity

The Investigator is responsible for assessing severity of each reported AE. The CTCAE Version 5.0 should be used to assess and grade AE severity.

Any event not described in the CTCAE V5.0 may be assigned as follows:

- Grade 1: Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Grade 2: Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Grade 3: Severe: An event that prevents normal everyday activities.
- Grade 4: Life-threatening consequences or urgent intervention indicated (must be reported as an SAE).
- Grade 5: Death related to adverse event (must be reported as an SAE).

8.4 Assessment of Causality

The possibility of a causal relationship between each AE and the study treatment should be assessed by the Investigator. The causal relationship can be classified as either:

- Related: There is a reasonable causal relationship between study drug administration and the AE.

  or

- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

If there is a reasonable possibility of a causal relationship between the event and the study treatment, i.e. if there are facts (evidence) or arguments to suggest a causal relationship, the AE is considered related to the study treatment and an adverse drug reaction (ADR).

Practical Guidance for Causality Assessments:

An adverse event will not be considered related to study treatment if it:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors.
- may be judged to be due to the patient's clinical state or therapy other than study treatment being administered.
- is not biologically plausible that the event is related to study medication.
- does not reappear or worsen when study treatment is re-administered.
- does not follow a temporal sequence from administration of study treatment.

An adverse event may be considered related to study treatment if it:

- follows a temporal sequence from administration of study treatment.
- is a known response to the investigational product based on clinical or preclinical data.
- could not be explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other therapy administered to the patient.
- disappears or decreases upon cessation or reduction of dose of study treatment.
- reappears or worsens when study treatment is re-administered.

8.5 Unexpected Adverse Event

An unexpected AE is not identified in nature, severity, or frequency in the current Reference Safety Information (RSI) or is of greater severity or frequency than expected based on the information in the respective RSI for the investigational product(s).

For the purpose of this study, the current Investigator Brochures (IBs) for pelareorep and avelumab will be used for assessment of expectedness.

8.6 Time Period for Collecting AEs and SAEs

After informed consent, but prior to initiation of study treatment (paclitaxel, pelareorep, and/or avelumab), only AEs/SAEs caused by a protocol-mandated intervention(s) will be collected (e.g., SAEs related to invasive procedures such as biopsies). All identified AEs and SAEs must be recorded and described on the appropriate page of the electronic Case Report Form (eCRF) and reported according to Section 8.9. AEs and SAEs must be collected after first treatment dose until 30 days from last dose of study drug or the initiation of non-protocol therapy after last dose of study drug, whichever comes first.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical/Surgical History or Signs and Symptoms, as applicable of the eCRF.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Oncolytics.

The Investigator must report all SAEs to Oncolytics within 24 hours of becoming aware, as indicated in Section 8.9.

SAEs that occur more than 30 days after the last dose of study treatment but while the patient is still considered on-study with intent to resume treatment (i.e. if study treatment is held for longer than 4 weeks but for fewer than 8 weeks) must be reported.

8.7 Documentation of AEs and SAEs

The Investigator is responsible for detecting, documenting, events that meet the definition of an AE or SAE and remains responsible for following up the events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study treatment.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.8 Follow-up of AEs and SAEs

The Investigator is required to proactively follow each participant at subsequent visits/contacts.

All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Any ongoing events that are considered to be “Related” to study treatment will be followed up until they are resolved or deemed to be chronic.

8.9 Reporting Serious Adverse Events

Serious adverse events (SAE) are defined in Section 8.2. The Investigator should inform Oncolytics of any SAE within 24 hours of being aware of the event, using the SAE Report Form provided for the study via email to <SAE_REO_028@oncolytics.ca> as per the instructions found in study materials provided to the site. If email is not feasible, the form should be faxed to +403-283-0858.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be provided as a follow-up SAE report. The Investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Investigators should also report event(s) to their IRB as required.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

NOTE: After study closure, study-drug related SAEs should be reported voluntarily by the treating physician to Oncolytics.

Serious adverse event reporting to regulatory authorities will be conducted by Oncolytics (or designee) in accordance with 21CFR312.32, local requirements and international regulations, as appropriate.

PrECOG will provide all participating Investigators with suspected unexpected serious adverse reaction (SUSAR) reports received from Oncolytics.

8.10 Special Situation Reports

8.10.1 COVID-19 Reporting

All positive COVID-19 test results must be reported with the type of test performed recorded.

Coding for COVID-19 adverse events will be as follows.

- Infections and infestations - Other, specify
- Specify = COVID-19

The categories and definitions of severity used for COVID-19 AEs are defined in Section 8.3.

COVID-19 adverse events that qualify as Serious Adverse Events per Sections 8.2 and 8.3 must be reported as such, per Section 8.9.The following information will be captured:

- Narrative: Identify all pertinent facts related to the COVID-19 infection including, but not limited to the following: Presumptive vs confirmed diagnosis. If presumptive, please update narrative if/when diagnosis is confirmed, including timelines.
    - Treatment information
    - Recovery information, including timelines
    - Outcome information/status

All deviations or withdrawals due to COVID-19 will documented as such in the eCRF.

8.10.2 Pregnancy and Lactation Exposure

Pregnancies, suspected pregnancies, and lactation exposures occurring after the first exposure to the study treatment, whether or not associated with AEs, will be reported by the Investigator to Oncolytics (SAE_REO_028@oncolytics.ca) within 24 hours of awareness, using the Pregnancy Report Form provided for the study. Study treatment is to be discontinued immediately. The Investigator will follow the patient until completion or termination of the pregnancy and must notify Oncolytics immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the mother sustained an adverse event (e.g. spontaneous abortion), the Serious Adverse Event Report should be submitted (Section 8.9) in addition to the Pregnancy Report Form.

If the foetus or child sustained any adverse events (e.g. congenital defects), the Parent-Child/Foetus Report Form should be submitted in addition to the Pregnancy Report Form. All neonatal deaths that occur within 28 days of birth, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the study treatment and any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment should be classified as a serious adverse event and reported to Oncolytics immediately (i.e., no more than 24 hours after learning of the event).

8.10.3 Overdose or Medication Errors

For this study, the administered doses of pelareorep, avelumab, and paclitaxel higher than the doses, defined in Section 5.0, whether accidental or intentional, will be considered as an overdose and protocol violation.

There is no recommended specific treatment for an overdose of pelareorep. Overdose of the avelumab and paclitaxel or medication errors will be managed at Investigator's discretion, reported to Oncolytics immediately and documented on the relevant AE eCRFs and reported as an SAE, if indicated. The patient is to be monitored until they have resolved or returned to a baseline level.

Signs, symptoms, or the clinical sequelae of a suspected overdoses or medication errors should be recorded as AEs in the eCRF. Serious signs, symptoms, or clinical sequelae of suspected overdoses or medication errors will be reported to Oncolytics according to Section 8.9.

8.11 Reporting of Other Second Primary Cancers

New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study. All cases of new primary cancers identified during the study, regardless of relationship to protocol treatment, must be reported to Oncolytics as serious adverse events. The recurrence or development of metastatic disease of cancer under the study is considered disease progression and not necessarily a serious adverse event.

NOTE: Once data regarding remission status are no longer required by the protocol, no follow-up data should be submitted.

9. Measurement of Effect

This is a Phase 2 study to guide the development and design of potential subsequent registration studies. Treatment effect will be examined in two ways:

Primary Endpoint:

- Efficacy in terms of overall response rate (ORR) at week 16 according to RECIST V1.1 (see Appendix II), assessed by the study investigator at each site.

Exploratory Endpoints:

- ORR per RECIST v 1.1 and OS at EOS.
- PFS per RECIST v 1.1.
- The biomarker analyses on this study will examine the immunological changes within the TME and peripheral blood in patients treated with paclitaxel alone, in combination with pelareorep, and in combination with pelareorep and avelumab.
    - As such, the pretreatment and on-treatment biopsies/blood collections are critical with mandatory blood draws and optional tumor biopsies. Key assays will:
        - Examine the expression of immune-related biomarkers, such as PD-1 and PD-L1.
        - Identify biological changes, as defined by changes in gene expression within the TME and PMBC, between pre-treatment and on-therapy specimens.
        - Compare changes in the T cell repertoire between pre-treatment and on-therapy tumor biopsies; examining common T cell clones between tumor tissue and peripheral blood samples.
        - Compare changes in the T cell repertoire between pre-treatment and on-therapy peripheral blood samples.
        - Examine tumor mutational burden and prevalent DNA mutations in all patients from cfDNA.

10. Study Parameters

1. All pre-study scans should be done ≤ 4 weeks prior to registration.
2. All other pre-study assessments should be done ≤ 2 weeks prior to registration.
3. Study treatment must be initiated ≤ 10 days after registration.
4. Assessments can be done as clinically indicated, in addition to the time points listed here.

Procedures	Screening	Cycle 1* (1 cycle=28 Days)								Cycle 2 -Cycle 4* (1 cycle=28 Days)								Cycle 5 and Subsequent Cycles*								Off Treatment[17]	Follow-Up[19]
	Days	1	2	3	8	9	15	16	17	1	2	3	8	9	15	16	17	1	2	3	8	9	15	16	17		
Windows (+/- days):	-14 to -1				2		2			2			2		2			2			2		2				
Written Informed Consent[0]	X																										
Disease Characteristics[1]	X																										
Medical/Surgical History	X																										
Assessment of Baseline Signs & Symptoms	X																										
Height	X																										
Physical Exam including Weight	X	X			X		X			X								X[16]								X	
Vital Signs (Temperature, Pulse, Blood Pressure)[2]	X	X	X		X	X	X	X		X	X		X	X	X	X		X[16]	X[16]		X[16]	X[16]	X[16]	X[16]		X	
ECOG Performance Status	X	X								X								X[16]								X	
Urinalysis[3,6]	X	X								X								X[16]								X	
CBC/Differential/Platelets[4,6]	X	X			X		X			X			X		X			X[16]								X	
Chemistry[5,6]	X	X			X		X			X								X[16]								X	
Endocrine (Cohort 3)[7]		X								X								X[16]									
PTT/INR	X																										
Lactate Dehydrogenase (LDH)	X																										
Serum Pregnancy Test[8]	X																										

Procedures	Screening	Cycle 1* (1 cycle=28 Days)								Cycle 2 -Cycle 4* (1 cycle=28 Days)								Cycle 5 and Subsequent Cycles*								Off Treatment[17]	Follow-Up[19]
	Days	1	2	3	8	9	15	16	17	1	2	3	8	9	15	16	17	1	2	3	8	9	15	16	17		
Optional Tumor Biopsy[9]	X								X[9]																		
Research Blood Specimens[10]		X			X					X								X									
CA15-3	X									X								X								X	
Pelareorep Administration[11] (Cohorts 2 + 3)		X	X		X	X	X	X		X	X		X	X	X	X		X	X		X	X	X	X			
Avelumab Administration[12] (Cohort 3)				X					X			X					X			X					X		
Paclitaxel Administration[13]		X			X		X			X			X		X			X			X		X				
Concomitant Medication Review[14]	X	X			X		X			X								X								X	
Adverse Events Assessment	X	X			X		X			X								X								X[18]	
Chest & Abdominal CT Scan, Bone Scan, and Other as clinically indicated[15]	X	Every 8 weeks until week 16, then every 12 weeks																									
Disease and Survival Status																											X

***** **Scheduled Visits:** +/- 2 day window for therapy/tests/visits during therapy (see Section 6). Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted (See 6.1).

0 A signed ICF must be obtained before any study-specific assessments are initiated. In the event that > 14 days elapse between the initial date of consent and C1D1, follow institutional policy regarding re-consent requirements.

1 Record date of diagnosis, primary tumor type, histology, and stage.

2 Patients will have Temperature, Pulse and Blood Pressure taken at Screening; Day 1, 8 and 15 of each visit; and at Off-Treatment visit. In addition, patients will have their blood pressure measured prior to each pelareorep infusion and 30 minutes (+/- 5 minutes) after completion of each pelareorep infusion in Cohort 2 and Cohort 3. After participants complete Cycle 4, only findings associated with an SAE or with an AE ≥ Grade 3 are to be captured in the CRF, with the

exception of Blood Pressure measurements before and after pelareorep administration.

3 For protein screen using spot testing; if >Grade 2 repeat with mid-stream urine; if still >Grade 2 then urine collection for 24 hours to confirm <2g/24hours (Grade 0, 1 or 2). Reduced urinalysis data will be collected after participants complete Cycle 4; see footnote 16.

4 CBC with differential and platelet count which includes WBC, ANC, Platelets, Hemoglobin, and Hematocrit required prior to each dose of paclitaxel. Reduced hematology data will be collected after participants complete Cycle 4; see footnote 16.

5 Albumin, BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin, and total protein. Reduced chemistry data will be collected after participants complete Cycle 4; see footnote 16.

6 Cycle 1, Day 1 labs do not need to be repeated if screening lab assessments were completed within 7 days prior. Laboratory samples can be drawn within 72 hours prior to study treatment administration.

7 Patients in Cohort 3 require additional monitoring for endocrine disorders and include assays for: adrenocorticotropic hormone (ACTH), serum cortisol, serum thyroxin, and thyroid-stimulating hormone (TSH). Perform every 2 cycles of treatment (Cycle 1, Day 1; Cycle 3, Day 1; Cycle 5, Day 1; etc.). Results are not required prior to treatment. If Avelumab is discontinued for any reason, additional lab monitoring is not required. Reduced endocrine data will be collected after participants complete Cycle 4; see footnote 16.

8 Required for sexually active females of child-bearing potential. Women who are not of child-bearing potential need documentation in their source.

9 **Optional:** Patients from each cohort (excluding safety run-in patients) may provide formalin-fixed paraffin-embedded (FFPE) tissue from a needle core biopsy collected prior to randomization (archival tissue allowed) and on-treatment from Cycle 1, collected between Days 17 and 28. See Section 13.1 for details.

NOTE: A maximum of 5 patients in each cohort will have biopsies collected.

10 Prior to treatment administration, collect one (1) 2 mL K2EDTA tube and two (2) 10 mL K2EDTA tubes. See Section 13.2 for details.

11 Patients will receive pelareorep by IV infusion on Days 1, 2, 8, 9, 15 and 16. In Cohorts 2 and 3, pelareorep is to be administered 30 minutes after completion of paclitaxel infusion on Days 1, 8 and 15. Patients may receive premedications prior to infusion. See Section 5 for dosing instructions and Section 6 for dose delays/modifications.

12 Patients will receive avelumab on Days 3 and 17. Patients may receive premedications prior to infusion. See Section 5 for dosing instructions and Section 6 for dose delays/modifications

13 Patients will receive paclitaxel on Days 1, 8, and 15. Patients may receive premedications prior to infusion. See Section 5 for dosing instructions and Section 6 for dose delays/modifications.

14 Includes review of all Concomitant medications taken within 30 days prior to randomization. Concomitant medications associated with an SAE or with any AE that the Investigator assesses to be immune-related must be entered in the eCRF. Steroids must also be entered. Vaccines are not permitted <14 days prior to C1D1 nor in first cycle of study treatment; inactivated vaccines administered after completion of Cycle 1 must be documented. No other concomitant medications need to be recorded.

15 Chest and Abdominal CT scan in order to obtain clinical tumor measurements. PET scans may not be used to assess response or progression; if PET CT was performed, the CT component may be used if CT was obtained per RECIST V1.1 guidelines for gap thickness. Bone Scan must be completed at Screening and repeated only if positive, per institutional standard of care. Tumor assessment to be performed every 8 weeks (± 7 days) for 16 weeks, then every 12 weeks from C1D1, regardless of dose interruptions or dose delays. Post-screening assessments should be performed using the same technique used at screening. Screening CT must be conducted ≤ 4 weeks prior to registration.

16 After participants complete Cycle 4, only findings associated with an SAE or with an AE ≥ Grade 3 must be recorded in the CRF. Laboratory values ≥ CTCAE Grade 3 must also be captured. Blood pressure measurements taken before and after pelareorep administration must still be captured.

17 The Off Treatment visit takes place when the decision to remove a patient from study treatment has been made. If patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression, initiation of a new therapy, or withdrawal of consent, whichever occurs first.

18 Patients will be followed for adverse events for 30 days after their last dose of study medication or the initiation of non-protocol therapy after last dose of study medication, whichever comes first. If the Off Treatment visit occurs ≤ 30 days after the patient's last dose of study treatment, the patient must be contacted by telephone at 30 days (up to 37 days) after the last dose of study treatment (or prior to initiation of subsequent therapy, whichever comes first) to assess AEs. However, a serious adverse event occurring at any time after discontinuation of study therapy that is felt to be at least possibly related to study therapy should be recorded.

19 When patients discontinue study treatment, they will be followed for survival status every 4-6 months until they have withdrawn consent, been lost to follow-up, died, or EOS is reached, whichever occurs first. If a patient discontinues study treatment for reasons other than progression, follow with regular tumor assessments per standard of care until progression, initiation of a new therapy, or withdrawal of consent, whichever occurs first.

11. Drug Formulation and Procurement

11.1 Pelareorep

11.1.1 Other Names

Reovirus type 3 Dearing

11.1.2 Classification

Immuno-oncolytic virus

11.1.3 Storage and Stability

Pelareorep may be stored at -20°C or ≤ -60°C for up to 72 months from date of drug product fill. Product should be maintained at whichever storage temperature is initially chosen when the product is received and should not be transferred between storage temperature conditions.

Upon receipt of shipment, the investigator or designee must confirm appropriate temperature conditions have been maintained during transit of pelareorep by inspecting the enclosed temperature device, as well as inspecting the contents for accuracy versus the packing list. Any discrepancies must be resolved before use of the study drug.

11.1.4 Dose Specifics

Pelareorep will be provided in glass vials. It is a clear to translucent colorless to light blue liquid containing $4.5x10^{10}$ $TCID_{50}$ of reovirus Serotype 3 – Dearing Strain per mL.

11.1.5 Preparation

The dilution or mixing will be done at the study sites. Vial labels will indicate the product, lot number, and concentration and will include all required regulatory label elements. Full instructions are provided in the study Pharmacy Manual.

The mixing and preparation procedures must be done in a biological safety cabinet (BSC) with appropriate precautions including mask, gown and gloves. All material that comes into contact with the viral preparation will be placed in sodium hypochlorite (800 ppm chlorine) or 70% ethanol and disposed of as biohazardous waste.

11.1.6 Route of Administration

Intravenous

11.1.7 Drug Interactions

See Pelareorep Investigator's Brochure.

11.1.8 Agent Availability

Pelareorep will be supplied by Oncolytics Biotech Inc. and distributed to sites by Oncolytics designated depot.

The initial supply of pelareorep will be sent directly to the site upon site activation. As needed, pelareorep may be requested by the Principal Investigator (or their authorized designees) at each participating institution. The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the receipt, disposition, and return/destruction (site's drug destruction policy must be reviewed and approved by PrECOG before any study drug can be destroyed at a site) of pelareorep.

11.1.9 Agent Ordering

Sites will be responsible for ordering drug for re-supply from Oncolytics.

11.1.10 Agent Accountability

Pelareorep will be stored in a secure location. Only authorized pharmacy and study staff will have access to this agent. Drug accountability will be verified by PrECOG.

11.1.11 Side Effects

See Pelareorep Investigator's Brochure

11.1.12 Nursing/Patient Implications

See Pelareorep Investigator's Brochure

11.2 Avelumab

11.2.1 Other Names

Bavencio®

11.2.2 Classification

Anti-PDL1 monoclonal antibody

11.2.3 Storage and Stability

BAVENCIO® (avelumab) Injection is a sterile, preservative-free, and clear, colorless to slightly yellow solution for intravenous infusion supplied as a single-dose vial of 200 mg/10 mL (20 mg/mL), individually packed into a carton.

Store refrigerated at 36°F to 46°F (2°C to 8°C) in original package to protect from light.

Do not freeze or shake the vial.

The vial stopper is not made with natural rubber latex.

11.2.4 Dose Specifics

200 mg/10 mL (20 mg/mL) solution in single-dose vial.

11.2.5 Preparation

- Visually inspect vial for particulate matter and discoloration. Avelumab is a clear, colorless to slightly yellow solution. Discard vial if the solution is cloudy, discolored, or contains particulate matter.
- Withdraw the required volume of avelumab from the vial(s) and inject it into a 250 mL infusion bag containing either 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride Injection.
- Gently invert the bag to mix the diluted solution and avoid foaming or excessive shearing.
- Inspect the solution to ensure it is clear, colorless, and free of visible particles.
- Discard any partially used or empty vials.

Storage of Diluted Avelumab Solution

Protect from light.

Store Diluted Avelumab Solution

At room temperature up to 25°C for no more than 8 hours from the time of dilution

or

Under refrigeration at 2°C to 8°C for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze or shake diluted solution.

11.2.6 Route of Administration

Administer the diluted solution over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron).

Do not co-administer other drugs through the same intravenous line.

11.2.7 Drug Interactions

See Avelumab Investigator's Brochure.

11.2.8 Agent Availability

Avelumab will be supplied by Oncolytics Biotech Inc. and provided to sites by Oncolytics designated depot.

The initial supply of avelumab will be sent directly to the site upon site activation. As needed, avelumab may be requested by the Principal Investigator (or their authorized designees) at each participating institution. The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the receipt, disposition, and return/destruction (site's drug destruction policy must be reviewed and approved by PrECOG before any study drug can be destroyed at a site) of avelumab.

11.2.9 Agent Ordering

Sites will be responsible for ordering drug for re-supply from Oncolytics.

11.2.10 Agent Accountability

Avelumab will be stored in a secure location. Only authorized pharmacy and study staff will have access to this agent. Drug accountability will be verified by PrECOG.

11.2.11 Side Effects

See Avelumab Investigator's Brochure.

11.2.12 Nursing/Patient Implications

See Avelumab Investigator's Brochure.

Please refer to the commercial package insert for full prescribing information.

11.3 Paclitaxel

Paclitaxel will be obtained by the individual study sites as standard of care treatments from commercial stock and is not an investigational product on this trial. Paclitaxel is generic and may be obtained from multiple manufacturers. Please refer to the commercial package insert for full prescribing information.

12. Statistical Considerations

This is an open-label randomized Phase 2, 3-cohort study for patients with HR+/HER2-, endocrine-refractory metastatic breast cancer. A total of 48 patients will be enrolled and will be treated until progression, unacceptable toxicity, withdrawal of consent, or EOS.

A three patient safety run-in will be conducted in Cohort 3 (pelareorep+avelumab+paclitaxel) prior to beginning randomization into all three cohorts.

Following the safety run-in, eligible patients will be randomized 1: 1: 1. Each cohort will enroll 15 patients. Patients will be stratified for visceral versus non-visceral metastatic disease and randomized to receive:

Cohort 1: Control group with dosing of weekly paclitaxel (PTX) according to standard of care (SOC)

Cohort 2: Investigate treatment with pelareorep added to SOC (PTX)

Cohort 3: Investigate treatment with pelareorep in combination with avelumab added to SOC (PTX).

12.1 Cohort 3 Safety Run-In

A three patient safety run-in will be conducted in Cohort 3 (pelareorep+avelumab+paclitaxel) prior to beginning randomization into all three cohorts. A safety evaluation will be conducted after all 3 patients have completed one cycle of treatment (i.e., received all the doses for all the drugs per protocol) or discontinued the therapy before completion of Cycle 1 due to toxicity (i.e., permanently discontinued or dose held). Patients who discontinue the therapy before completion of Cycle 1 due to reason other than toxicity will be replaced. Refer to Table 5-1 for criteria for DLT.

During the safety review a Steering Committee will review all the safety data captured during the first cycle of treatment and make recommendations to continue, alter, or permanently suspend the study based on this analysis. The Steering Committee may recommend amendments to explore alternate dosing schedules or lower doses based on the overall toxicity experience, even if the criteria for DLT are not met.

12.2 Analysis Populations

Full Analysis Set

The Full Analysis set (Intention-to-Treat or ITT set) comprises all patients who are enrolled into the Safety Run-in or randomized to treatment.

Randomized Analysis Set

The Randomized Analysis set comprises all patients who were randomized to a study treatment arm.

Safety Analysis Set

The Safety Analysis set comprises all patients who received any amount of study treatment.

Full Response Evaluable Set

The Full Response Evaluable set comprises all patients with measurable disease on the baseline tumor assessment who received any amount of study treatment and have at least 1 post-baseline radiographic tumor assessment.

Randomized Response Evaluable Set

The Randomized Response Evaluable set comprises all patients with measurable disease on the baseline tumor assessment who were randomized to a study treatment arm, received any amount of study treatment, and have at least 1 post-baseline radiographic tumor assessment.

12.3 General Considerations

Continuous variables will be summarized using mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Time to event variables will be summarized using the Kaplan-Meier method. Where appropriate, confidence intervals around point estimates will be presented, and estimates of the median and other quantiles, as well as individual time points (for time to event data) will be produced.

All confidence intervals will be 2-sided at the 80% level.

12.4 Efficacy Analyses

ORR at week 16 and EOS will be analyzed using the Full Analysis set, the Randomized Analysis set, the Full Response Evaluable set, and the Randomized Response Evaluable set. OS and PFS will be analyzed using the Randomized Analysis set and the Full Analysis set.

The study is not powered to make comparisons between treatment arms. Statistical tests, if performed, will be considered exploratory. Comparative results will be summarized descriptively, and consistency in trends in clinical and biological effects will be evaluated across clinical and biomarker endpoints, to provide an overall assessment of the relative benefits of each treatment.

Tumor response rates in each arm will be reported with category counts, percentage, and confidence intervals using the Clopper-Pearson method for individual treatment groups. Comparison of tumor response rates between groups will be based on a difference in proportions and confidence intervals using a normal approximation with continuity correction. Further analyses using logistic regression, exploring potentially influential covariates, may be performed.

12.5 Biomarker Analyses

Patients in the Safety Analysis Set who have relevant blood or tissue sampling will be included in the biomarker analyses.

Biomarker endpoints will be summarized by treatment group at baseline and at each applicable post-baseline time point, and compared between treatment groups at post-baseline time points. Changes from baseline will also be summarized by group and compared between groups.

Comparisons between groups will use difference of means for continuous variables (e.g., T cell clonality, diversity, TMB), and difference of proportions and/or odds ratios for categorical or clinically relevant discretizations of continuous variables (e.g., high/low clonality).

Univariate and multivariate modeling will be performed to characterize the strength of association between biomarker measures (or discretizations thereof) and clinical outcomes.

12.6 Sample Size Considerations

The sample size for this Phase 2 exploratory study is based on practical considerations to enable the assessment of safety, tolerability, and preliminary biological and clinical activity. As formal tests of statistical significance are not planned, power calculations will not be performed.

The level of uncertainty around between-group comparisons on the key clinical endpoint of ORR can be quantified in terms of the width of the confidence interval for the treatment effect: with 15 patients per arm, the 80% confidence interval for the difference in ORR between

treatment arms will have half-width of about 28%. This quantity is commensurate with the anticipated magnitude of difference expected in the comparison of Cohort 1 vs Cohort 2 (about 25% difference expected) and Cohort 1 vs Cohort 3 (about 50% difference expected).

12.7 Additional Analyses

Demographic and baseline characteristics will be summarized using data from all patients in the Full Analysis (ITT) set and in the Safety Analysis set by treatment group. Treatment exposure, including duration on treatment and extent of exposure, will be summarized by treatment group.

Safety analysis will include summaries by treatment group of: AEs, laboratory measures, physical examinations, and vital signs using data from patients in the Safety Analysis set.

13. Laboratory and Pathology Correlative Studies

Biomarkers on this study will examine the immunological changes within the TME and peripheral blood in patients treated with paclitaxel alone, in combination with pelareorep, and in combination with pelareorep and avelumab.

As such, the pretreatment and on-treatment biopsies/blood collections are critical with mandatory blood draws and optional tumor biopsies. Key assays will:

- Examine the expression of immune-related biomarkers, such as PD-1 and PD-L1.
- Identify biological changes, as defined by changes in gene expression within the TME and PBMCs, between pre-treatment on-therapy specimens.
- Compare changes in the T cell repertoire between pre-treatment and on-therapy tumor biopsies; examining common T cell clones between tumor tissue and peripheral blood samples.
- Compare changes in the T cell repertoire between pre-treatment and on-therapy peripheral blood samples.
- Examine tumor mutational burden and prevalent DNA mutations in all patients from cfDNA.

13.1 Correlative Studies: Optional Tumor Samples

Patients from each cohort (excluding safety run-in) may provide formalin-fixed paraffin-embedded tissue from a needle core biopsy collected prior to randomization (archival tissue allowed) and on-treatment from Cycle 1, collected between days 17 and 28.

NOTE: A maximum of 5 patients in each cohort will have biopsies collected.

13.1.1 Pathology Sample Processing and Shipment

Sites should submit Formalin-Fixed Paraffin-Embedded (FFPE) tumor tissue blocks (preferred) or up to 15 unstained FFPE slides (2 sections per slide) plus H&E slide from a tumor tissue block. Thickness of the sections should be at 4-5 micron.

A copy of the pathology report from initial diagnosis and/or subsequent tumor sampling should be sent when the sample is shipped. If a pathology report is not available for the subsequent tumor sample completed for research purposes only, it is acceptable not to provide. Samples should be shipped **Monday-Thursday**. Samples will be shipped ambient via overnight courier.

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Kits will be supplied. Instructions and shipping address will be provided.

13.2 Correlative Studies: Mandatory Peripheral Blood Samples

Blood draws for biomarker analyses will be performed prior to treatment administration on Cycle 1 Day 1, Cycle 1 Day 8, and on Day 1 of all remaining cycles.

13.2.1 Peripheral Blood Sample Processing and Shipment

Instructions, shipping labels, supplies and address will be provided in the kits.

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Blood Sample Processing:

Draw whole blood into (1) 2 mL K2EDTA tube and (2) 10 mL K2EDTA tubes. The draw tube should be at room temperature 18°C to 25°C prior to collection.

After collection, the sample must be immediately inverted 8 to 10 times.

2 mL K2EDTA Tube

Immediately store 2 mL K2EDTA tube at -20°C. Tube can also be stored at ≤ -70°C (preferably -80°C) long term.

Cycle 1, Day 1; Cycle 1 Day 8 and Cycle 2 Day 1 samples for each patient will be shipped to the Central Biorepository Pathology Facility (CBPF) once all 3 samples are available on a patient. Remaining samples will be batch shipped approximately every 3 months to the CBPF for storage.

2 x 10 mL K2EDTA Tubes

****Process sample within 4 hours of collection****

- Gently mix blood sample by inversion 10 times (do not shake).
- Place tube immediately on wet ice for 5 minutes.
- Centrifuge at 1200 relative centrifugal force (RCF) for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RCF for 15 minutes). Immediately place the tube on wet ice after centrifugation.

After centrifugation, the plasma layer will be at the top half of the tube. The nucleated cells (WBC) will be in a whitish layer, called the "buffy coat", just under the plasma and above the red blood cells.

Plasma Preparation:

- Using a transfer pipette take the top two-thirds of the plasma and transfer plasma into a 15 mL conical centrifuge tube, be careful not to disturb the buffy coat layer in the EDTA tube (**NOTE:** see below for buffy coat processing instructions). Centrifuge the 15 mL conical tube at 1200 RCF for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RCF for 15 minutes). Immediately place the conical tube on wet ice after centrifugation.
- Transfer equal amounts of plasma into two (2) properly labeled polypropylene tubes for cryopreservation being careful not to disturb the small PBMC/pellet.
- Store the two aliquots of plasma samples in the freezer at ≤ -70°C (preferably -80°C) until they are shipped to central lab.

Buffy Coat Preparation:

- From the EDTA tube remove and aliquot the "buffy coat"; be careful not to disturb the layer of red blood cells.
- Store the aliquot of cells in one (1) properly labeled polypropylene tube for cryopreservation.
- Store the sample in the freezer at ≤ -70°C (preferably -80°C) until it is shipped to central lab.

Plasma and buffy coat samples should be batched together and shipped approximately every 3 months. Individual patients should only be included in the shipment if all of their samples have been completed. Samples should be shipped **Monday-Thursday**. Samples must be shipped on dry ice via overnight courier.

14. Administrative

14.1 Protocol Compliance

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with and be prepared by PrECOG and/or representatives. The Investigator should not implement any deviation or change to the protocol or consent without prior review and documented approval from PrECOG and/or representatives and the Institutional Review Board (IRB) of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

If a deviation or change to the approved protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, notification will be submitted to the IRB for review and approval as soon as possible afterward. Documentation of approval signed by the chairperson or designee of the IRB(s) should be in the study records. If PrECOG and/or representatives provides an amendment that substantially alters the study design or increases the potential risk to the patient; the consent form must be revised and submitted to the IRB(s) for review and approval; the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the Amendment; and the new form must be used to obtain consent from new patients prior to study entry. Information as to whom Investigators should send correspondence will be provided in additional study documents.

14.2 Institutional Review Board (IRB)

Before study initiation, the Investigator must have written and dated approval from their respective IRB for the protocol, consent form, patient recruitment materials/process and any other written information to be provided to patients. The Investigator should also provide the IRB with a copy of the Investigator's Brochure or product labeling, and any updates.

The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, amendments, and administrative letters) according to regulatory requirements, IRB or study site procedures.

14.3 Informed Consent Procedures

Investigators must ensure that patients who volunteer for clinical trials or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other information.

A protocol specific informed consent form (ICF) template will be provided to sites. Preparation of the site-specific consent form is the responsibility of the site Investigator and must include all applicable regulatory and IRB requirements, and must adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. All changes to the ICF template will be approved by PrECOG and/or their representatives prior to implementation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow PrECOG and/or its agents, regulatory authorities, and the IRB of record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in the informed consent form or other approved form obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by

the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the trial. The investigator is responsible for assuring adequate documentation of this process and for storage and maintenance of the original signed consent form for each patient/patient.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

14.4 Safety Communication

Investigators will be notified of all AEs that are serious, unexpected, and related to the investigational product(s). Upon receiving such notices, the Investigator must review and retain the notice with the Investigator's Brochure and submit a copy of this information to the IRB according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

14.5 Monitoring

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of investigational product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator and verify that the facilities remain acceptable. Monitoring of drug accountability will also occur.

The study may be evaluated by other auditors and government inspectors who must be allowed access to electronic Case Report Forms (eCRFs), source documents and other study files. The Investigator must notify PrECOG of any scheduled visits by regulatory authorities and submit copies of all reports. Information as to who investigators should notify of an audit or where to address questions will be provided in additional study materials.

14.6 Study Records

An Investigator is required to maintain adequate regulatory files with corresponding communication and approvals, accurate histories, observations and other data on each individual treated. Full details of required regulatory documents will be provided in additional study materials. Data reported on the eCRFs must be consistent with the source documents as part of the patient record.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). A unique identifier will be assigned to each patient, and any patient records, samples (e.g. blood, urine, or tumor tissue) or datasets that are transferred to the sponsor or vendor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

A study specific signature record will be maintained to document signatures and initials of all persons at a study site who are authorized to make entries and/or corrections on eCRFs as well as document other study-specific roles.

14.7 Electronic Case Report Form (eCRF) Information

Additional information regarding eCRF instructions, timelines for data entry/ submission and query completion can be found in supplemental materials provided to the site. Sites will be expected to complete eCRFs as per the schedule provided and submit all relevant data as per the specified timelines. All items recorded on eCRFs must be found in source documents.

The completed eCRF must be promptly reviewed, electronically signed, and dated by the Principal Investigator.

Instructions for management of patients who do not receive any protocol therapy:

If a patient is registered and does not receive any assigned protocol treatment, baseline data will be entered. No data past baseline will be collected. Document the reason for not starting protocol treatment on the appropriate electronic off treatment form.

14.8 Records Retention

FDA Regulations (21CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents for the periods described below for studies performed under a US Investigational New Drug (IND):

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the Sponsor of the discontinuation of trials and that an application will not be submitted.

The Investigator must retain investigational product disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, whichever is longer. The Investigator must contact PrECOG and/or representatives prior to destroying any records associated with the study.

Information as to who investigators should contact for questions will be provided in additional study documents. PrECOG and/or representatives will notify the Investigator when the trial records for this study are no longer needed.

14.9 Publication Policy

The Sponsor/PrECOG recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. Written approval from the Sponsor and PrECOG is required before disclosing any information related to this clinical trial, and no publications initiated by Investigators may be published until all protocol defined primary and exploratory endpoints are published in a manuscript. Investigators in this study agree to have their name listed as an Investigator in any publication reporting results from this study, whether or not they are an author on the publication.

The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between the Sponsor and PrECOG and the Task Order between PrECOG and the institution of the Investigator.

14.10 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Oncolytics. All study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Oncolytics may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Oncolytics may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Safety or ethical issues.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study treatment development.

15. References

Adams, S. et al., 2018. Atezolizumab Plus nab-Paclitaxel in the Treatment of Metastatic Triple-Negative Breast Cancer With 2-Year Survival Follow-up: A Phase 1b Clinical Trial. JAMA oncology.

Berman, A.T., Thukral, A.D., Hwang, W.T., Solin, L.J. and Vapiwala, N., 2013. Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment. Clin Breast Cancer, 13(2): 88-94.

Brockton, N.T. et al., 2015. The Breast Cancer to Bone (B2B) Metastases Research Program: a multi-disciplinary investigation of bone metastases from breast cancer. BMC Cancer, 15: 512.

Dirix, L.Y. et al., 2018. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat, 167(3): 671-686.

Gutierrez, A.A. et al., 2017. Pooled data analysis of the safety and tolerability of intravenous Pelareorep in combination with chemotherapy in 500 + cancer patients. Annals of Oncology. 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376.

Heinemann, L. et al., 2011. Synergistic effects of oncolytic reovirus and docetaxel chemotherapy in prostate cancer. BMC Cancer, 11: 221.

Herrinton, L.J. et al., 2005. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol, 23(19): 4275-86.

International Agency for Research on Cancer, 2012. Breast cancer: estimated incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.

Jackson, G.G., Muldoon, R.L., Johnson, G.C. and Dowling, H.F., 1963. Contributions of Volunteers to Studies on the Common Cold. Am Rev Respir Dis, 88: SUPPL 120-7.

Jackson, G.G.M., R. L.; Cooper, G. S.;, 1961. Reovirus type 1 as an etiologic agent of the common cold. Journal of Clinical Investigation, 40(6): 1022-1072.

Jarudi, N.I., Huggett, D.O. and Golden, B., 1973. Reovirus keratoconjunctivitis. Can J Ophthalmol, 8(2): 371-3.

Lerner, A.M., Cherry, J.D., Klein, J.O. and Finland, M., 1962. Infections with reoviruses. N Engl J Med, 267: 947-52.

Marcato, P., Dean, C.A., Giacomantonio, C.A. and Lee, P.W., 2009. Oncolytic reovirus effectively targets breast cancer stem cells. Mol Ther, 17(6): 972-9.

Minuk, G.Y., Paul, R.W. and Lee, P.W., 1985. The prevalence of antibodies to reovirus type 3 in adults with idiopathic cholestatic liver disease. J Med Virol, 16(1): 55-60.

Minuk, G.Y. et al., 1987. Reovirus type 3 infection in patients with primary biliary cirrhosis and primary sclerosing cholangitis. J Hepatol, 5(1): 8-13.

Mostafa, A.A. et al., 2018. Oncolytic Reovirus and Immune Checkpoint Inhibition as a Novel Immunotherapeutic Strategy for Breast Cancer. Cancers (Basel), 10(6).

National Cancer Institute, N.I.o.H., U.S. Department of Health and Human Services, 2014. SEER Cancer Statistics Review 1975-2011. http://seer.cancer.gov/archive/csr/1975_2011/.

Norman, K.L. et al., 2002. Reovirus oncolysis of human breast cancer. Hum Gene Ther, 13(5): 641-52.

O'Shaughnessy, J., 2005. Extending survival with chemotherapy in metastatic breast cancer. Oncologist, 10 Suppl 3: 20-9.

Rosen, L., Evans, H.E. and Spickard, A., 1963. Reovirus infections in human volunteers. Am J Hyg, 77: 29-37.

Rosen, L., Hovis, J.F., Mastrota, F.M., Bell, J.A. and Huebner, R.J., 1960. An outbreak of infection with a type 1 reovirus among children in an institution. American Journal of Epidemiology, 71(2): 266-274.

Sabin, A.B., 1959. Reoviruses. A new group of respiratory and enteric viruses formerly classified as ECHO type 10 is described. Science, 130(3386): 1387-9.

Sei, S. et al., 2009. Synergistic antitumor activity of oncolytic reovirus and chemotherapeutic agents in non-small cell lung cancer cells. Mol Cancer, 8: 47.

Siegel, R.L., Miller, K.D. and Jemal, A., 2016. Cancer statistics, 2016. CA Cancer J Clin, 66(1): 7-30.

Smith, I., 2006. Goals of treatment for patients with metastatic breast cancer. Semin Oncol, 33(1 Suppl 2): S2-5.

Sundquist, M., Brudin, L. and Tejler, G., 2017. Improved survival in metastatic breast cancer 1985-2016. Breast, 31: 46-50.

Torre, L.A. et al., 2015. Global cancer statistics, 2012. CA Cancer J Clin, 65(2): 87-108.

Tyler, K.L. and Fields, B.N., 1990. Reoviruses. In: B.N. Fields and D.M. Knipe (Editors), Virology. Raven Press Ltd, New York, pp. 1307-1328.

World Health Organization, 2013. Projections of mortality and causes of death, 2015 and 2030. http://www.who.int/healthinfo/global_burden_disease/projections/en/.

Appendix I ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix II: RECIST Version 1.1

Malignant Disease Evaluation

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline Version 1.1. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.

The term evaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

- **Measurable**

  Measurable tumor lesions are those 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:

  - ≥ 10 mm by CT scan (irrespective of scanner type) and MRI (*no less than double the slice thickness and a minimum of 10 mm*)
  - ≥ 10 mm caliper measurement by clinical exam (when superficial)
  - ≥ 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung)

  If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

- **Malignant Lymph Nodes**

  To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis (perpendicular to longest diameter) when assessed by CT scan.

- **Non-Measurable**

  All other lesions (or sites of disease), including small lesions not meeting the criteria in “Measurable” and “Malignant Lymph Nodes” above, are considered non-measurable lesions. This includes lymph nodes measured at ≥ 10 to <15 mm in the short axis. **NOTE:** Lymph nodes measured at <10 mm in the short axis are considered normal.

  Lesions considered to be non-measurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

  NOTE: ‘Cystic lesions’ that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

  ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability in "Measurable" above. Blastic bone lesions are non-measurable.

Tumor lesions that are situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Definitions of Response

- **Target Lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameters), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

The sum of the target lesions (longest diameter for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters/axes will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- Complete Response (CR)

  The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

- Partial Response (PR)

  At least a 30% decrease in the sum of the diameters/axes of target lesions, taking as reference the baseline sum diameters/axes. To be assigned a status of partial response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response is met.

- Progressive Disease (PD)

  At least a 20% increase in the sum of the diameters/axes of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm over the nadir. (**NOTE:** the 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/axes while on study. (**NOTE:** a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease).

  To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

- **Non-Target Lesions**

All other lesions or sites of disease including any measurable lesions over and above the 5 target lesions and lymph nodes measured at ≥ 10 to <15 mm in the short axis 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 unequivocal progression of each should be noted throughout follow-up.

- Complete Response (CR)

  The disappearance of all non-target lesions and normalization of tumor marker levels, if applicable. All lymph nodes must be non-pathological in size (<10 mm short axis). To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

  NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

- Non-CR/Non-PD

  The persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker levels above the normal limits. To be assigned a status of Non-CR/Non-PD, measurements must have met the Non-CR/Non-PD criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

- Progressive Disease (PD)

  The appearance of one or more new lesion(s) and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

  When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

  When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

  Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

- **Evaluation of New Lesions**

  The appearance of new lesions constitutes Progressive Disease (PD).

- **Symptomatic Deterioration**

  Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Evaluation of Patient’s Best Overall Response

The best overall response is the best response recorded from the start of the treatment until confirmed disease progression or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (Table V-1).

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed ≥ 4 weeks after the criteria for response are first met.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of ≥ 4 weeks.

Table II-1: Overall Response for All Possible Combinations of Tumor Response

Target Lesions	Non-Target Lesions	New Lesion	Overall Response	Remarks
CR	CR	No	CR	Confirmation at ≥ 4 weeks
CR	Non-CR/Non-PD*	No	PR	Confirmation at ≥ 4 weeks
CR	Not Evaluated	No	PR	Confirmation at ≥ 4 weeks
PR	Non-PD*/Not Evaluated	No	PR	Confirmation at ≥ 4 weeks
SD	Non-PD*/Not Evaluated	No	SD	Documented at least once ≥ 4 weeks from study entry
Not All Evaluated	Non-PD	No	Not Evaluable	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD*	
Any	Any	Yes	PD	

* PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to Non-Target Lesions-Progressive Disease for further explanation.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

NOTE: If patients respond to treatment and are able to have their disease resected; the patient's response will be assessed prior to the surgery. However, the patient will be considered inevaluable for survival analysis.

Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality should be used throughout the study to measure disease (preferred but not mandated). Below is a list of methods that may be used depending on location and type of cancer.

- **Clinical Lesions**

  Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- **CXR**

  Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- **CT and MRI**

  This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

  Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized

for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **PET-CT**

  At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- **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 concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Endoscopy, Laparoscopy**

  The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

- **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.

- **Cytology, Histology**

  These techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is mandatory to differentiate between response or SD (an effusion may be a side effect of the treatment) and PD.

Appendix III: NYHA Classification

Class	Symptoms
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath), or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford Textbook of Internal Medicine. Vol. 2, pp 2228. Oxford University Press. 1997	

Appendix IV: Investigator's Statement

1. I have carefully read this protocol entitled **"**A study to assess overall response rate by inducing an inflammatory phenotype in Metastatic **BR**east c**A**n**CE**r with the Oncolytic Reovirus Pe**L**areor**E**p in Combina**T**ion with anti-PD-L**1** Avelumab and Paclitaxel – **BRACELET-1** Study**", Version 3.0 dated 07/21/2022 (Protocol Number PrE0113)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.
2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.
3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.
4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.
5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from PrECOG, LLC unless this requirement is superseded by the FDA.

Principal Investigator (PI):

PI Name: _____

Site Name: _____

Signature of PI: _____

Date of Signature: _______________

MM DD YYYY