Statistical Analysis Plan

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Date	18 August 2022

A study to assess overall response rate by inducing an inflammatory phenotype in Metastatic BReast cAnCEr with the Oncolytic Reovirus PeLareorEp in CombinaTion with anti-PD-L1 Avelumab and Paclitaxel – BRACELET-1 Study

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SPONSOR:	Oncolytics Biotech Inc 4660 La Jolla Village Dr. Ste. 850 San Diego, CA 92122
PREPARED BY:	Andrew Ricchezza Biostatistician Quality Data Services, Inc.

SIGNATURES/APPROVAL PAGE

AUTHORS

DocuSigned by:
Andrew Ricchezza
90B656C4FE2741F...

07 Sep-2022

Andrew Ricchezza
Biostatistician
Quality Data Services, Inc.

Date

APPROVERS

DocuSigned by:
Fengmin Zhao
BED3511CE49640F...

(-Sep-2022

Fengmin Zhao, PhD
Statistician
PrECOG, LLC.

Date

DocuSigned by:
Paul Catalano
A0FF674252E6477...

0 - ep-2022

Paul Catalano ScD.
Statistician
PrECOG, LLC.

Date

DocuSigned by:
Thomas Heineman
33F3F173168B46A...

- ug-2022

Thomas C. Heineman, MD, PhD
Global Head of Clinical Development and Operations
Oncolytics Biotech (U.S.) Inc

Date

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
APC	Antigen Presenting Cell
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
C	Celsius
CA 15-3	Carcinoma Antigen 15-3
CBC	Complete Blood Count
cfDNA	Cell Free DNA
CI	Confidence Interval
CIVI	Continuous IV Infusion
COVID-19	Coronavirus Disease 2019
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
dsRNA	Double-Stranded RNA
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
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
G	grams
GCP	Good Clinical Practice
HER	Human Epidermal Growth Factor Receptor
HR	Hormone Receptor
HR	Hazard Ratio
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IMAE	Immune-Related Adverse Event
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat
IV	Intravenous(ly)
kg	Kilogram
L	Liters
LDH	Lactate Dehydrogenase
LV	Leucovorin
m^2	Square Meter
Max	Maximum
Min	Minimum
mBC	Metastatic Breast Cancer
MDSC	Myeloid Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MHC	Major Histocompatibility Complex
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
n	Number
NACT	New Anti-cancer Therapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PET	Positron Emission Tomography
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PR	Partial Response
PT	Preferred term
PTT	Partial Thromboplastin Time

PTX	Paclitaxel
RECIST	Response Evaluation Criteria in Solid Tumors
Reovirus	Respiratory Enteric Orphan Virus
RNA	Ribonucleic Acid
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SD	Standard Deviation
SOC	Standard of Care
SOC	System Organ Class
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
TFLs	Tables, Figures and Listings
TNBC	Triple Negative Breast Cancer
TME	Tumor Microenvironment
ULN	Upper Limit of Normal
US	United States
vs	Versus
WBC	White Blood Count
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of Child Bearing Potential
XRT	Radiation Therapy

2. INTRODUCTION

2.1. Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) describes the planned analysis of the safety and efficacy data from this study. A detailed description of the planned table, figure, and listing (TFLs) outputs is provided in the accompanying TFL template document.

The intent of this document is to provide guidance for the analysis of data related to safety, efficacy, and blood and tumor biomarkers. In general, the analyses come directly from the protocol, unless they have been modified by agreement between the Sponsor and Quality Data Services, Inc. (QDS). A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TFL templates. That information is not a synopsis of the study and does not require review or approval because it is simply extracted from the protocol. Attached signatures indicate approval of the statistical analysis sections of the SAP, as well as accompanying TFL templates. These sections must be agreed upon prior to database lock. This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the appropriate section of the clinical study report. Any substantial deviations from this SAP will be agreed upon between the sponsor and QDS. Deviations from this SAP, both substantial and non-substantial, will be documented in the clinical study report. Any updates to the analyses, study designs, and TFL presentations after this SAP is finalized and approved will be documented in a running Note to the SAP document.

3. STUDY OBJECTIVES

This is an exploratory Phase 2 study with the purpose to inform the design of a subsequent registration study. All objectives are exploratory objectives.

3.1. Study Objectives

3.1.1. Primary Objective

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

3.1.2. Exploratory Objectives

- Examine efficacy in terms of overall survival (OS) and ORR at End of Study (EOS) according to RECIST V1.1.
- Examine efficacy in terms of progression-free survival (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 tumor microenvironment (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; examine 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).

4. STUDY DESIGN

4.1. General Study Design and Plan

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. EOS 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.

A three-patient safety run-in will be conducted in Cohort 3 (pelareorep + avelumab + paclitaxel) prior to beginning the enrollment and randomization of the remaining 45 patients across all three cohorts.

Following the safety run-in, eligible patients will be randomized 1: 1: 1. Each cohort will enroll 14-16 patients. The randomized study is expected to accrue 45 patients in total. All randomized patients will be included in the analyses. 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: Investigational treatment with pelareorep added to SOC (PTX)
Cohort 3: Investigational treatment with pelareorep in combination with avelumab added to SOC (PTX).

4.2. Study Population

Female patients with Hormone Receptor+ (HR+)/Human Epidermal Growth Factor Receptor 2 negative (HER2-) 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.

4.3. Treatment Administration

4.3.1. Cohort 3 safety run-in

Before randomization, a three-patient safety run-in will be conducted in Cohort 3 (pelareorep + avelumab + paclitaxel). A safety evaluation will be conducted after all 3 patients have completed one cycle of treatment or discontinued the therapy due to toxicity in cycle 1. Patients who discontinued therapy for reasons other than toxicity in cycle 1 will be replaced.

A Steering Committee will review all the safety data captured from the first cycle of study treatment in the safety run-in and then make recommendations to continue or suspend the study. The Steering Committee may also suggest altering the treatment schedule or dosage.

There is a Dose-Limiting Toxicity (DLT) Evaluation for events occurring during the first cycle of study treatment of the Safety Run-In (Protocol Table 5-1).

The safety run-in was completed on September 21 2020 and, following Steering Committee review of the first cycle safety data, the randomized part of the study was opened to enrollment on October 22 2020, prior to the update to Version 2.0 of the protocol. None of the modifications to the protocol were made because of the Steering Committee review of the first cycle safety data.

4.3.2. Randomization

After the safety review, the eligible patients will be randomized 1: 1: 1 in 3 cohorts. Patients will be stratified for visceral versus non-visceral metastatic disease. Each cohort will enroll 14-16 patients.

Each site will log onto electronic Data Capture (eDC) system to retrieve their patient randomization treatment assignment.

4.3.3. Study treatment

Cohort 1: Paclitaxel (PTX).

- PTX 80 mg/m^2 IV infusion on Day 1, 8, and 15 during a 28-day cycle.

Cohort 2: PTX + Pelareorep.

- PTX 80 mg/m^2 IV infusion on Day 1, 8, and 15 during a 28-day cycle.
- Pelareorep 4.5 x 10^{10} $TCID_{50}$ IV infusion on Day 1, 2, 8, 9, 15 and 16 in all 28-day cycles. 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 3: PTX + Pelareorep + Avelumab.

- PTX 80 mg/m^2 IV infusion on Day 1, 8, and 15 during a 28-day cycle.
- Pelareorep 4.5 x 10^{10} $TCID_{50}$ IV infusion on Day 1, 2, 8, 9, 15 and 16 in all 28-day cycles.
- Avelumab 10 mg/kg (not more than 800 mg) IV infusion on days 3 and 17 in all 28-day cycles. 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.

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

4.3.4. Dose Modifications and Treatment Discontinuation

A +/-2 day window is allowed for scheduled therapy, required tests and/or visits except as otherwise noted. Dose delays >2 days will be considered missed and will not be replaced.

In the event of high toxicity, the treatment will be delayed until the patient recovers. 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.

Reasons that a patient may discontinue treatment in this clinical study are considered to constitute one of the following:

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.

Patients who discontinue study treatment for reason(s) other than progression should be followed for response assessments until progression per RECIST v 1.1, start of new treatment, or withdrawal of consent, whichever occurs first.

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

5. TREATMENT EFFECT MEASUREMENTS AND ANALYSIS

Measurements of treatment effect will be examined via tumor response rate, progression-free survival, overall survival, and biomarker analyses.

5.1. Tumor Response Rate

Investigator-assessed disease response (per RECIST V 1.1) based on each tumor assessment during the study period will be used in the evaluation of best response for each patient. The primary efficacy endpoint of overall response rate (ORR) at 16 weeks is based on the number of patients with a best response of either CR or PR at the Week 16 tumor assessment. Confirmed responses per RECIST V. 1.1 are not required for the primary efficacy analysis but are required for the best overall response analysis at EOS**.**

5.2. Progression-Free Survival

Progression-free survival is defined as the time from randomization, or enrollment for non-randomized safety run-in patients, to the first documented disease progression per RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Subjects with no post-baseline tumor assessment will be censored on the date of randomization or enrollment. Details of the censoring is discussed in Section 7.5.2.

5.3. Overall Survival

Overall survival at EOS is an exploratory efficacy endpoint for this study. This endpoint is based on the all-cause mortality rate through EOS; that is, 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. Survival data will be collected through EOS, where possible, for all patients, as those who discontinue study treatment will be followed by phone 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.

5.4. Biomarker Analyses

Oncolytics is responsible for all biomarker analyses. These analyses are therefore outside of the scope of this SAP and will be explained in a separate Plan for Biomarker Data Management and Statistical Analysis.

6. SAFETY MEASUREMENTS

Safety will be evaluated by

- Adverse events
- Concomitant medications and procedures
- Clinical laboratory tests
- Physical examination findings and medical history
- Vital signs measurements

6.1. Adverse Events

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.

After informed consent, but prior to initiation of study treatment, only AEs/SAEs caused by a protocol-mandated intervention(s) will be collected. After the initiation of study treatment and until 30 days after the last protocol treatment administration, all identified AEs must be recorded in electronic Case Report Form (eCRF).

All AEs that occurred on or after the date of study treatment will be considered Treatment-emergent AEs.

6.1.1 Serious Adverse Event

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.

All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

6.1.2 AE Severity

The Investigator is responsible for assessing severity of each reported AE. CTCAE V5.0 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 a SAE).

6.1.3 Assessment of AE Causality

The possibility of a causal relationship between an AE and each of the study treatments should be assessed by the Investigator. The causal relationship can be classified as either related or not related.

6.2. Concomitant Medications and Procedures

Concomitant medications (taken to treat SAEs, IMAEs [immune-related adverse events] and steroids) and procedures will be collected during the trial and recorded in the CRF page. Vaccines are not permitted <14 days prior to Cycle 1, Day 1 nor during first cycle of study treatment; however, inactivated vaccines may be administered after completion of Cycle 1 and will be recorded in the CRF, if administered.

6.3. Clinical Laboratory Assessments

Clinical laboratory tests will be collected at screening and during the study per the protocol schedule.

6.4. Physical Examination and Medical History

Physical examination findings will be collected at screening and during the study per the protocol schedule. Medical and surgical history will also be collected during screening.

7. GENERAL STATISTICAL CONSIDERATIONS

This section will go into detail about the statistical approaches and methodology for the study analyses. Statistical analysis and programming of tables and listings will be conducted by QDS, using SAS® Release 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

7.1. Study Design and Sample Size 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.

The sample size is based on practical considerations to enable the assessment of safety, tolerability, and preliminary biological and clinical activity. Formal tests of statistical significance are not planned, and power calculations will not be performed. Given the exploratory nature of this study, overall response, safety, and correlative biomarker results will be used as the key qualitative decision drivers that may inform any subsequent study.

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 40% difference expected).

7.2. Analysis Methodology

There will be two analyses: a Primary Efficacy analysis conducted when the last patient enrolled reaches Week 16, and a Final analysis conducted at EOS. All data entered up to the cutoff for the Primary Efficacy

analysis will be cleaned and soft-locked prior to conducting that analysis. The shell Tables and Listings will be the same for the Primary and EOS analyses, except for Tables 14.2.5-14.2.10 and Figures 14.2.11-14.2.12, which report ORR and OS at EOS. These Tables will only be produced for the EOS analysis.

Similarly, Tables 14.2.1-14.2.4 which report ORR at Week 16 will not be reprogrammed during the Final analysis.

Continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical data will be summarized with frequencies 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.

In general, listings will be presented by patient. Tables will be summarized and presented by specific analysis populations.

7.3. Analysis Populations

7.3.1. 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.

7.3.2. Randomized Analysis Set

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

7.3.3. Safety Analysis Set

The Safety Analysis set comprises all patients who received any amount of study treatment. Patients in this population who in addition have relevant blood or tissue sampling will be included in the biomarker analyses.

7.3.4. 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.

7.3.5. 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.

7.4. Safety Analysis

The safety evaluations include AEs, concomitant medication, clinical laboratory assessments, vital signs, and physical examination. Safety analysis will be assessed for the Safety Analysis set.

7.4.1. Disposition

Patient disposition will be presented for the Full Analysis Set.

Disposition data (e.g. treated patients, reasons for discontinuation, etc.) will be summarized descriptively by cohort for the patients enrolled into the study.

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. Data collected on screen failures is not included in the Tables and Listings.

7.4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented for two analysis populations: the Full Analysis set and the Randomized Analysis set.

Baseline is defined as the last measurement before study treatment.

Demographic and baseline characteristics data will be summarized descriptively (number of patients (frequency), mean, SD, median, minimum, and maximum) by cohort for Full Analysis Set and Randomized Analysis Set.

7.4.3. COVID-19-Related Forms

Protocol deviations related to COVID-19 precautions or suspected or actual COVID-19 infections will be presented in a listing separate from the listing of all other protocol deviations. Similarly, details of patient withdrawal from treatment or from the study for any reason related to COVID-19 will be presented in a listing separate from the subject disposition listing which includes the reasons for patient withdrawal from treatment and from the study as collected on the End of Treatment and End of Study CRF pages. The number of subjects who withdraw from treatment and the number of subjects who withdraw from the study due to COVID-19-related reasons will be summarized by Cohort for the Full Analysis Set and Randomized Analysis Set. The details of any positive viral and antibody coronavirus test results and any COVID-19 vaccinations each will be presented in data listings.

7.4.4. Medical and Surgical History

Medical and surgical history data collected during screening will be summarized by cohort for Full Analysis Set and Randomized Analysis Set.

7.4.5. Concomitant Medications and Procedure

Concomitant medications and procedures will be recorded on the CRFs. Concomitant medications collected will be limited to steroids, vaccines (allowed only after Cycle 1), and medications associated with serious or immune-related adverse events. All concomitant medications will be coded to a World Health Organization Drug Dictionary (WHO-DD) term.

Concomitant medications will be summarized by cohort for the Safety Analysis set. In the summary table, the number and percentage of patients taking each medication will be presented by ATC Level 2 Classification (therapeutic subgroup).

7.4.6. Physical Exam

The physical exam CRF collects what date and time physical examinations are performed and the reasons for not done. There will be no data listing and summary analysis for physical exam since all abnormal findings are stored in medical history or adverse event forms.

7.4.7. Adverse Events

Treatment-emergent AEs (TEAEs) are those that occur after administration of the first study dose and until 30 days after the last dose of treatment. In the case where the start date of the AE is unknown, it will be assumed to be treatment-emergent. TEAEs will be summarized by System Organ Class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®). MedDRA version V23.1 will be used. The frequency of patients who experience TEAEs will be summarized by cohort in the Safety Analysis Set. Patients with more than one occurrence of the same AE will be counted only once for the corresponding PT. Patients with more than one AE within a SOC will be counted only once within the SOC.

All TEAEs, treatment-related AEs, SAEs, treatment-related SAEs, TEAEs resulting in study treatment modification, TEAEs leading to early study discontinuation, and fatal TEAEs will be summarized by each cohort. SAEs will also be summarized by median time from study treatment start to event onset within cohort for each MedDRA preferred term. Dose limiting toxicities will be summarized for safety run-in subjects in Cohort 3.

Adverse event severity will be graded according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). TEAEs will be summarized by maximum severity and cohort.

7.4.8. Clinical Laboratory Data

Numeric clinical laboratory data will be summarized at baseline and for each post-baseline visit, by cohort, using descriptive statistics. Non-numeric laboratory tests will be summarized separately using frequency counts on unique responses. Individual change from baseline in lab values will be calculated and summarized descriptively by cohort. The laboratory shift from baseline to the worst laboratory value after treatment during the study will be displayed for each laboratory test and by cohort. The laboratory shift tables will show normal range shift and toxicity grade shift.

The worst laboratory value for normal range shift will be derived as follows:
If an abnormal test has only one direction, either decrease or increase, then the value farthest from the normal in that direction will be taken as the worst value.
if an abnormal test has 2 directions, both decrease and increase, subject will be evaluated to find the worst decrease and the worst increase separately for this test. The normal range shift table will represent the worst decrease and worst increase for this test.
The post-baseline worst laboratory values will be used for the normal range shift table.

The worst laboratory toxicity grade will be derived as follows:

The values of eligible laboratory tests will be assigned toxicity grades based on CTCAE v5.0. Results from eligible tests conducted at each study visit will be assigned a grade, and the highest grade assigned to any post-baseline result will be taken as the worst toxicity grade. Subjects who experienced the same highest grade for the same test at different visits will only be counted once.

7.4.9. Vital Signs Data

Vital sign collected value and change from baseline will be summarized by visit and displayed by cohort. Change in blood pressure from before pelareorep infusion to 30 minutes after infusion will be summarized by study day and cohort for subjects in Cohorts 2 and 3.

7.5. Efficacy Analysis

7.5.1. Tumor response rate analysis

ORR (CR+PR) at week 16 and at EOS will be analyzed using the Full Analysis set, as well as in the Randomized Analysis Set, Full Response Evaluable set, and Randomized Response Evaluable set. The Randomized Analysis Set will be the primary dataset for this analysis.

Overall response rate (ORR) at week 16 is defined as a response assessment of partial or complete response (i,e., PR or CR) documented via radiographic evidence at the scheduled week 16 imaging assessment. Similarly, Disease Control Rate at week 16 is defined as a complete response, partial response, or stable disease assessment documented via radiographic evidence at the week 16 imaging assessment. Confirmed responses per RECIST V. 1.1 are not required for this analysis.

The tumor response rate analyses at EOS of ORR and Disease Control Rate will be based on best overall response; that is, each subject's best tumor response after start of study treatment and at or before EOS; confirmed responses per RECIST V 1.1 are required for this analysis. All assessments of tumor response and best overall response are performed in accordance with the response category definitions defined in Appendix II of the clinical study protocol.

ORR (CR+PR) rates and Disease Control Rate (CR+PR+SD) in each cohort 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 cohorts will be based on a difference in proportions and confidence intervals using a normal approximation with continuity correction.

All confidence intervals will be 2-sided at 80% level. Formal testing of statistical significance is not planned in this exploratory study.

Further analyses using logistic regression, exploring potentially influential covariates, may be performed.

7.5.2. PFS analysis

Table 1 outlines two PFS censoring rules that will be performed as applicable. Kaplan-Meier method will be used to estimate the median, 25th, and 75th percentiles of time to PFS, the rate of PFS at 6, 12 months or other time points of interest. Cox proportional hazards model will be used to estimate the

hazard ratios (the unadjusted HR for cohort and an HR for cohort where the stratification factor is visceral vs. non-visceral disease; if additional factors are needed, they will be ad hoc).
Point estimates will be accompanied by 80% 2-sided confidence intervals. PFS analysis will be performed based on the Randomized Analysis Set. To include the patients in the safety run-in, PFS analysis based on the Full Analysis Set may be performed.

Table 1.Progression Free Survival Censoring Rules

	PFS primary analysis	PFS sensitivity analysis
No PD, No death	Censored at last tumor assessment	Censored at last tumor assessment
PD or death after 1 missed tumor assessment	PFS event at the date of PD or death	PFS event at the date of PD or death
PD or death after 2 or more missed tumor assessments	Censored at last tumor assessment prior to PD or death	PFS event at the date of PD or death
PD or death after NACT	Censored at the last tumor assessment prior to NACT	PFS event at the date of PD or death
No PD, no death, NACT initiated	Censored at the last tumor assessment prior to NACT	Censored at last tumor assessment regardless of NACT
Abbreviations: PD = progressive disease; PFS = progression-free survival; NACT = new anticancer therapy		

7.5.3. Overall survival analysis

Overall survival will be defined as the time to death from any cause starting at registration for Safety run-in patients and randomization for all other patients. Patients who withdraw consent or are lost-to-follow-up will be censored at the date of last contact. All other patients still alive will be censored at EOS. The Kaplan-Meier method will be used to estimate the median and 25^{th} and 75^{th} percentiles of time-to-all-cause death by cohort for the Randomized Analysis Set and the Full Analysis Set at EOS. For each of the point estimates of survival time, the associated 80% 2-sided confidence interval will be presented. The Kaplan-Meier survival curve will be plotted by cohort.

7.5.4. Biomarker Analyses

The details of biomarker analysis are provided in the Biomarker Data Management and Analysis Plan.

7.6. Handling of Missing, Unscheduled, and Duplicated Data

All attempts will be made to prevent any missing values. Missing or invalid data will be treated as missing, not imputed.

No data imputation will be done for safety parameters except for the adverse events (AEs) with missing starting date.

AEs with incomplete start date will be considered treatment emergent if

- Day and month are missing, and the year is equal to or after the year of the first date of study treatment
- Day is missing and the year is after the year of the first dose date of study treatment
- Day is missing and the year is equal to the year of the first dose date of study treatment and the month is equal to or after the year of the first dose date of study treatment
- Year is missing
- Start date is completely missing

However, if the end date of the AE is before the first dose date of study treatment, the AE will not be treatment emergent regardless of the completeness of its start date.

If the relationship between AE and study medications (PTX or pelareorep or avelumab) is missing, then the “related” is assigned in the AE analysis.

The unscheduled data will not be reported unless specified otherwise. If there are more than one measurement at a given timepoint, the closest-to-target timepoint data will be reported.

7.7. Interim Analysis

As described in Section 7.2, a Primary Efficacy analysis will be conducted when the last patient enrolled reaches Week 16. The Final analysis will be conducted at EOS. The rolling biomarker analyses will be performed by Oncolytics per the Biomarker Data Management and Analysis Plan.

8. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

No changes are planned.

9. REPORTING CONVENTIONS

The mean and median will be displayed to one decimal place greater than the original value and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using SAS® Release 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

The following standards will be used in the data presentation:

- Section 14 tables should be in landscape format. Output should adhere to US / International Conference on Harmonization (ICH) margins and should not require changes for European page size. For item 14 tables, a blank row will separate the header from the content of the table listing. For tables that have "n (%)", the placement should be centered below "N=xx" in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.

- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If "%" is part of the column heading, do not repeat the "%" sign in the body of the table. Unless specified otherwise, "%" should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, leave the corresponding percentage blank.

- The format for minimum and maximum should be "Min, Max". SD should be the default for representing scale, unless standard error has been specified. Standard deviation should be abbreviated as "SD", and presented next to the mean value, without any +/- sign. The SD should have one additional decimal place beyond that of the mean (e.g. mean has one decimal place, SD should have two).

- "N" will represent the entire treatment group for the population group being analyzed, while "n" will represent a subset of the treatment group. For tables with population designated as a row heading, "N" should be used (i.e. tables where all participant data is not available for every variable within a treatment group). As a guideline, if the number is used in a denominator it should be presented as "N". If the number is used in the numerator, it should be presented as an "n".

- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number.

- All data listings will be sorted by Patient Number and time point (if applicable).

- The date format for all dates is DDMMMYYYY.

A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

10. REFERENCES

References are provided in the protocol.

11. TABLES, FIGURES, AND LISTINGS

See separate template document.

12. APPENDIX

12.1. Appendix 1. Study procedure and 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																											

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		
Serum Pregnancy Test[8]	X																											
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 Protocol Section 6). Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted (See Protocol Section 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 Protocol 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 Protocol 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 Protocol Section 5 for dosing instructions and Protocol Section 6 for dose delays/modifications.

12 Patients will receive avelumab on Days 3 and 17. Patients may receive premedications prior to infusion. See Protocol Section 5 for dosing instructions and Protocol 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 Protocol Section 5 for dosing instructions and Protocol 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.

12.2. Appendix 2. Overall Response for All Possible Combinations of Tumor Response

Table III-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.

13. DOCUMENT HISTORY

Version Date	Version	Modified By	Summary of Changes
2020-09-24	Final V 1.0	N/A	N/A. Initial version.
2021-09-12	**Draft V 2.0**	**Andrew Ricchezza**	**Updated study design and data collection sections per revisions from V1.2 to 2.0 of the protocol. Listings of COVID-19-related forms (deviations, withdrawals, vaccinations, and testing) were added to the analysis. Overall survival analysis on ITT population and Tumor response analysis at EOS for ITT and Response Evaluable populations were added.**
2022-1-17	**Draft V 2.0**	**Andrew Ricchezza**	**Overall survival analysis on Randomized Analysis Set (ITT analysis without the [non-randomized] run-in subjects) and Tumor response analysis at Week 16 and EOS for Randomized Analysis Set and Randomized Response Evaluable Set (ITT and evaluable analyses without the [non-randomized] run-in subjects) were added.**