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Statistical Analysis Plan Cover Page

Document Title: Statistical Analysis Plan for Protocol CD07_TNBC

Protocol Number: CD07_TNBC

Protocol Title: A Phase Ib/II Study of Leronlimab (PRO 140) Combined with Carboplatin in Patients with CCR5+ Metastatic Triple Negative Breast Cancer

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STATISTICAL ANALYSIS PLAN
FOR PROTOCOL CD07_TNBC

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Protocol Number:	CD07_TNBC	
Protocol Title:	A Phase Ib/II Study of Leronlimab (PRO 140) Combined with Carboplatin in Patients with CCR5+ Metastatic Triple Negative Breast Cancer (mTNBC)	
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SAP Version:	SAP –Version 0.1
SAP Date:	10 Aug 2021

I have read and approve the Statistical Analysis Plan specified above and agree on its content:

Statistician, [redacted]	Date
CytoDyn, Inc.	Date

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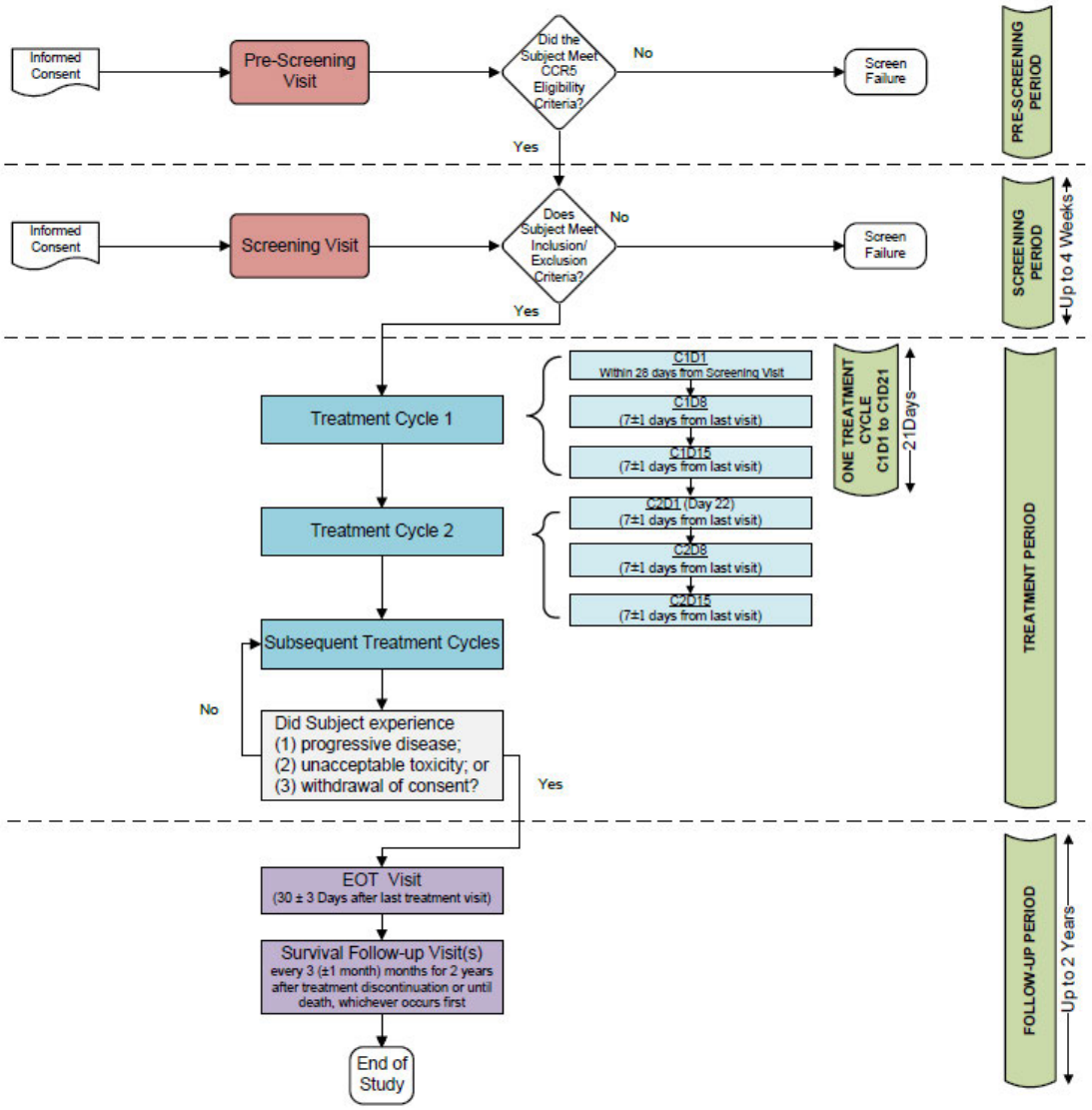


ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Transaminase
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
EOT	End of Treatment
DSMB	Data Safety Monitoring Board
DLT	Dose Limiting Toxicities
DSMB	Data Safety Monitoring Board
FDA	U.S. Food and Drug Administration
FUV	Follow-up Visit
GCP	Good Clinical Practice
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
MTD	Maximum Tolerate Dose
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
SAE	Serious Adverse Event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SD	Stable Disease
SOP	Standard Operating Procedure
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event
TTNM	Time to New Metastasis
TV	Treatment Visit

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for the clinical trial protocol CD07_TNBC, sponsored by CytoDyn, Inc. The reader of this SAP is encouraged to review the complete protocol, as this plan contains only a limited overview of protocol information. The main objective of the plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of efficacy data from this trial.

The format and content of this SAP are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All analyses planned and presented in this SAP will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents were reviewed in preparation of this Statistical Analysis Plan:

- Final protocol 4.0/ 20-Jan-2021
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

2. PROTOCOL DESIGN

2.1 Design Overview

Phase Ib

Phase Ib is a dose escalation phase with 3 dose levels (cohorts) of leronlimab (PRO 140) administered in combination with a fixed dose of carboplatin at AUC 5. This dose finding portion of study will follow a "3+3" designed to determine the maximum tolerated dose (MTD) of leronlimab (PRO 140) administered as subcutaneous injection in subjects with histologically confirmed mTNBC that express CCR5. The MTD is defined as 1 dose level (cohort) below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants.

A schematic of the "3 + 3" Dose Escalation Study Design is provided in Appendix 2.

Cohorts of 3 patients are entered at given dose level K. If no patients have a DLT, then the dose will be escalated to the next dose level, K +1. If more than 1 subject has a DLT then the previous dose level, K-1, will be considered as MTD. If 1 subject has a DLT an additional 3 patients will be treated at this dose level, K. If no further subjects suffer a DLT then the dose level will be escalated to K+1 and if any further subjects have a DLT then the previous dose level, K-1, will be considered the MTD. The MTD will be the maximum dose level with an observed toxicity rate of 0% or 17%.

If any of the SAEs or DLTs outlined above have occurred, the Data Safety Monitoring Board (DSMB) will conduct an independent review of the data and make a final decision for dose escalation to the next cohort.

The final decision on the MTD will be made following a review of the study data by the DSMB. Continuation into Phase II of the study will take place after the DSMB meeting.

Once the MTD has been determined, subjects enrolled in lower dose cohorts will be allowed to escalate the dose to the MTD, if acceptable per the Investigator's discretion.

Phase II

Phase II is a single arm study with 30 patients in order to test the hypothesis that the combination of carboplatin AUC 5 intravenously and MTD of leronlimab (PRO 140) SC will increase PFS in patients with CCR5 + mTNBC. PFS in patients with newly recurred TNBC is approximately 5 months.

Leronlimab (PRO 140) will be administered subcutaneously at a weekly MTD dose determined in the Phase Ib portion of the study and carboplatin target of AUC 5 every 3 weeks as combination therapy until disease progression or intolerable toxicity. A de-escalation dose of carboplatin will be allowed based on the toxicity, efficacy evaluation, and clinical judgment by physician.

In both the Phase Ib and Phase II portions of the study, patients will be evaluated for response at the end of 2 cycles (i.e., every 6 weeks) for the first 6 cycles (18 weeks) and at end of every 3 cycles (i.e., every 9 weeks) thereafter, and at EOT by CT, PET/CT or MRI with contrast (per treating investigator's discretion) using the same method as at baseline. Tumor measurements will be done using RECIST v1.1.

The total study duration for each subject consists of pre-screening, screening, treatment, and follow-up periods. A study flow diagram is presented in Appendix 3.

(1) Pre-Screening Period: A separate Informed Consent Form (ICF) will be used for the pre-screening. The pre-screening period is designed for evaluation of histologically confirmed diagnosis of mTNBC (documented by HER-2 negative, ER<1%, PR<1%) and CCR5 positive status by Immunohistochemistry (IHC) assay. This assay will be performed in archival tissue from previous biopsy specimens. If archival tissue is not available then, fresh core or excisional biopsy will be done. If patient qualifies, then they will undergo full screening.

(2) Screening Period: Screening assessments will commence after obtaining signed informed consent, and will include review of medical and medication history, demographic information and baseline disease characteristics, eligibility evaluation, physical examination, vital signs, height and weight, concomitant medications, electrocardiogram (ECG), tumor imaging assessment, routine serum biochemical, hematologic, urinalysis, serum pregnancy (if applicable). These assessments must be conducted within 28 days of the first treatment visit.

(3) Treatment Period: Subjects who meet the eligibility criteria will have completed following evaluations and assessments before receiving treatment: a) review of medical and medication history; b) physical examination, vital signs and documentation of ECOG performance status; c) ECG; d) routine serum biochemical, hematologic, urine pregnancy (if applicable) and urine laboratory assessments. Additionally, a blood sample will be collected prior to treatment administration for CTCs PD-L1/CCR5, and CTC - CAMLs analysis.

Each treatment cycle will consist of 21 days. Leronlimab (PRO 140) will be administered subcutaneously weekly on Days 1, 8, and 15 in combination with carboplatin AUC 5 on Day 1 of each cycle (every 21 days). Day 1 of Cycle 2 begins at Day 22. The study treatment will be administered by a licensed medical professional at clinic site or self-administered by subjects at home.

Subjects will be allowed to continue treatment under subsequent treatment cycles until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent.

(4) Follow-Up Period: An End of Treatment (EOT) visit will be conducted 30 (± 3) days after the last treatment visit (i.e., after last dose of leronlimab (PRO 140) and carboplatin). Additionally, follow-up will be done for survival status, by clinic visits or phone or another method of contact, every 3 months (±1 month) for 2 years after treatment discontinuation or until death, whichever occurs first.

2.2 Clinical Trial Treatments

2.2.1 Dosing Regimen

Phase Ib

• 350 mg leronlimab (PRO 140) SC weekly + AUC 5 Carboplatin every 3 weeks

• 525 mg leronlimab (PRO 140) SC weekly + AUC 5 Carboplatin every 3 weeks

• 700 mg leronlimab (PRO 140) SC weekly + AUC 5 Carboplatin every 3 weeks

Phase II

Leronlimab (PRO 140) will be administered subcutaneously at a weekly MTD dose determined in the Phase Ib portion of the study and carboplatin target of AUC 5 every 3 weeks as combination therapy until disease progression or intolerable toxicity. A de-escalation dose of carboplatin will be allowed based on the toxicity, efficacy evaluation, and clinical judgment by physician.

2.2.2 Duration of treatment:

- **Pre-Screening Period**: N/A (no pre-defined window period)
- **Screening Period**: Up to 4 weeks
- **Treatment Period**: Each treatment cycle consists of 3 weeks (21 days)
  *Subsequent Treatment Cycles: Subjects will be eligible for continuing treatment beyond first cycle in absence of disease progression or unacceptable toxicity or withdrawal of consent
- **Follow-Up Period**: In both the Phase Ib and Phase II portions of the study, the follow will be done up to 2 years after treatment discontinuation or until death, whichever occurs first

2.2.3 Randomization and Stratification

Randomization and Stratification is not applicable.

2.2.4 Blinding

Blinding is not applicable.

2.3 Protocol Objective(s)

Phase Ib

Primary Objectives:

- To determine the safety, tolerability and maximum tolerate dose (MTD) of leronlimab (PRO 140) when combined with carboplatin in patients with CCR5+ mTNBC.

Secondary Objective:

- To determine the recommended Phase II dose for the combination of leronlimab (PRO 140) and carboplatin in patients with CCR5+ mTNBC.

Phase II

Primary Objective:

- To evaluate the impact on progression-free survival (PFS) of the combination leronlimab (PRO 140) and carboplatin in patients with CCR5+ mTNBC.

Secondary Objectives:

- To assess the overall response rate (ORR) and clinical benefit rate (CBR) of carboplatin – leronlimab (PRO 140) combination in patients with CCR5+ mTNBC
- To assess benefit, based on time to new metastasis (TTNM)
- To assess the change in circulating tumor cells (CTCs) number after treatment; and
- To assess the safety and tolerability of the combination of leronlimab (PRO 140) and carboplatin in subjects with CCR5+ mTNBC.

2.4 Outcome Measures

2.4.1 Primary Outcome Measure

Phase Ib

- Maximum Tolerated Dose (MTD) by evaluation of dose-limiting toxicities (DLTs) of leronlimab (PRO 140) when combined with carboplatin AUC5.

  Note: The MTD is defined as 1 dose level below the dose in which dose limiting toxicities (DLTs) were observed in ≥ 33% of the participants during Cycle 1.

Phase II

- Progression free survival (PFS) defined as time in months from the date of first study treatment to the date of disease progression or death from any cause, whichever comes first.

  Note: All patients who receive at least one dose of leronlimab (PRO 140) and carboplatin combination will be included in the primary analyses of PFS. The Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria will be used for objective tumor response assessment (when disease is measurable and non- measurable);

  The time in months from start of treatment to progression or death will be measured for all patients who receive at least one dose of study drug. Patients will be followed up to 2 years after completion of treatment.

2.4.2 Secondary Outcome Measures

Phase Ib

- The number, frequency, and severity of adverse events (AEs) collected from the time of first treatment until 12 weeks after study treatment completion to evaluate safety of leronlimab (PRO 140) and carboplatin in subjects with CCR5+ mTNBC.

  Note: Adverse events will follow National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Phase II

- PFS according to RECIST v1.1 in participants with Detectable Programmed Death-Ligand 1 (PD-L1)

  Note: The PD-L1 expression testing will be performed at baseline. Breast tissue (primary or metastatic site) collected to analyze for the presence of CCR5 at pre-screening will additionally be used for evaluating PD-L1 expression levels.

- Overall response rate (ORR, defined as Complete Response (CR) + Partial Response (PR)), and clinical benefit rate (CBR, defined as CR + PR + Stable Disease (SD)) in subjects with CCR5+ mTNBC treated with leronlimab (PRO 140) and carboplatin.

  Note: Overall response rate defined as the proportion of patients who achieve an overall response of complete response or partial response in the total number of evaluable patients, assessed by RECIST v1.1. Clinical benefit rate is defined as the proportion of patients who achieve an overall response of complete response or partial response or stable disease in the total number of evaluable patients, assessed by RECIST v1.1. Imaging scans to be done at the end of 2 cycles (i.e., every 6 weeks) for the first 6 cycles (18 weeks) and at the end of 3 cycles (i.e., every 9 weeks) thereafter.

- Time to new metastases (TTNM);

  Note: Recorded time from baseline metastatic disease (at time of enrollment) to the time of development of new metastasis in different site. New metastases in same site will be also recorded.

- The change from baseline in circulating tumor cells (CTC) level in the peripheral blood.

  Note: Reported unit of measure will be the number of CTCs/milliliter. CTCs enumeration will be performed at baseline and at the time of response assessment. Fraction of baseline positive and change from ≥5 CTCs will be recorded and reported.

- Overall survival defined as time in months from the date of first study treatment to the date of death;

  Note: Patients will be followed from the start of treatment until 2 years post-treatment or death, whichever occurs first, and average survival time will be measured.
- The number, frequency, and severity of AEs collected from the time of first treatment until 12 weeks after study treatment completion to evaluate safety of leronlimab (PRO 140) and Carboplatin in subjects with CCR5+ mTNBC.

2.4.3 Exploratory Outcome Measures

- Measure immune biomarkers (PD-L1) in CTCs, metastatic tissue and immune cells such as CAMLs and correlate with therapeutic benefit (PFS); and
- Correlation between CCR5 expression (CTCs, CAMLs) and PD- L1 expression.

2.5 Safety Assessments

Safety will be assessed by close monitoring and timely assessment of adverse events (AEs), laboratory parameters (blood tests, urinalysis), vital signs (blood pressure, heart rate), subject's medical condition (physical examination including weight), general well-being and activities of daily life (Eastern Cooperative Oncology Group (ECOG) performance status). Each subject will be regularly assessed in each cycle for potential AEs and disease related signs and symptoms. The CTCAE v5.0 will be used to grade toxicities/AEs.

3. SAMPLE SIZE DETERMINATION

This is a Phase Ib/II, multicenter study that will enroll up to 18 subjects in Phase Ib and 30 subjects in Phase II of the study. The sample size for Phase Ib is based on conventional 3+3 study design and Phase II is based on clinical judgment. No statistical power calculation is used to establish the sample size.

4. INTERIM ANALYSIS/DSMB

No interim analysis (IA) will be performed for efficacy. There will be a safety review, once all three (or six) subjects from each cohort complete the DLT evaluation period (defined as cycle 1 or the first 21 days of treatment).

The Sponsor's Medical Monitor, CRO Medical Monitor and study investigators must be satisfied with data obtained in Cohort A before allowing subsequent enrollment of Cohort B. Likewise, they

must be satisfied with data obtained in Cohort B before allowing subsequent enrollment in Cohort C.

In addition, should any of the following events occur in any cohort during the DLT evaluation period, the Data Safety Monitoring Board (DSMB) will meet to review available study data and make a final decision for dose escalation to the next cohort:

a. Death in any subject in which the cause of death is judged to be possibly, probably or definitely related to leronlimab (PRO 140)
b. The occurrence in any subject of an anaphylactic reaction to leronlimab (PRO 140)
c. The occurrence in any subject of a severe local injection site reaction (Grade 3 which is not resolved or recurs; or Grade 4) that precludes administration of consecutive leronlimab (PRO 140) doses.
d. The occurrence in any subject of a life-threatening SAE whose causal relationship to leronlimab (PRO 140) is judged to be probable or definite
e. The occurrence of one or more non-life-threatening SAEs whose causal relationship to leronlimab (PRO 140) is judged to be definite
f. The occurrence, in one or more subjects, of Grade 4 laboratory abnormalities, judged to be probably or definitely related to receipt of leronlimab (PRO 140)
g. The occurrence of hematologic and non-hematological adverse events, judged to be possibly, probably or definitely related to receipt of leronlimab (PRO 140) based on previous clinical experience and that are of CTCAE Grade 3 or greater severity. Permissible exceptions to this rule include Grade 3 fatigue of less than one week duration, and Grade 3 nausea, vomiting, and diarrhea that resolve within 48 hours following institution of appropriate supportive care.
h. Hy's law
i. Neutropenic fever
j. Grade 4+ neutropenia or thrombocytopenia >7 days
k. Grade 3+ thrombocytopenia with bleeding
l. Grade 3+ electrolyte abnormality that lasts >72 hours, unless the patient has clinical symptoms, in which case all grade 3+ electrolyte abnormality regardless of duration should count as a DLT. Grade 3+ amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT

m. For patients with hepatic metastases, AST or ALT >8xULN or AST or ALT >5x ULN for ≥14 days.

5. HYPOTHESIS TO BE TESTED

There is no formal hypothesis testing for this study as the study is an initial Phase Ib/II evaluation and is intended to be hypothesis generating. The study is not powered to reliably yield statistically significant conclusions.

6. ANALYSIS POPULATIONS

6.1.1 Intent-to-Treat (ITT) Population

The ITT population is defined as the set of subjects who have received at least one dose of leronlimab (PRO 140) and have measurable disease at baseline. The ITT population will be used as the primary analysis population.

6.1.2 Per Protocol (PP) population

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population requirements, were not associated with any major protocol violations and have received at least 2 cycles of treatment. This population will be identified before the database lock. The PP analysis of primary and secondary outcome measures will be considered supportive.

6.1.3 Safety Population

The Safety Population will include all subjects who have received one dose of leronlimab (PRO 140). This population will be used for the analysis of safety parameters or measurements.

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value before the first treatment.

7.2 Duplicate Data

For unplanned duplicate data within a protocol-specified visit duration, the last measured value will be used for the analysis. If it is not possible to identify the “last measured value” the average of the duplicate values will be used.

7.3 Handling of Missing Data

All data will be used as observed, and no imputations will be made for any missing data point. All summaries will be based on observed data only.

7.4 Sensitivity Analysis

There will be no sensitivity analysis for this Phase Ib/II study.

7.5 Multicenter Clinical Trials

This is a multi-center clinical trial.

7.6 Multiple Comparisons and Multiplicity

There will be no adjustment for any multiple comparisons for this Phase Ib/II study.

7.7 Covariates and Prognostic Factors

No covariates are planned for this study.

7.8 Stratification Factors and Subgroups

There are no stratification factors or subgroups for this trial.

7.9 Standard Calculations

7.9.1 Age

Age will be calculated as the number of completed years between the date of informed consent and the subject's birth date.

Age (years) = integer of[(date of informed consent – date of birth)/ 365.25]

7.9.2 Change from Baseline

Change will be calculated using post baseline data and baseline data according to the formula noted below.

Change from Baseline = Post Baseline Data – Baseline Data

7.9.3 Time to event

Time to event will be calculated according to the formula noted below:

Time to event = (Date of Event – Date of first treatment) + 1

8. STATISTICAL METHODS

All data from this clinical trial will be provided in data listings, study drug, clinical trial center, subject, and time point (if applicable).

Data summary will be according to the variable type:

- Continuous data summaries will include:
    - Number of observations, mean, standard deviation, median, and minimum and maximum values.

- Categorical data summaries will include:
    - Frequency counts and percentages.

8.1 Summarizing and Tabulating the Collected Data

8.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects who sign an informed consent to participate in this study. The following will be summarized:

- The number of subjects who are signed informed consent
- The number of subjects received treatment in phase Ib
- The number of subjects received treatment in phase II
- The number of subjects who completed treatment in phase Ib
- The number of subjects who completed treatment in phase II
- The number of subjects who discontinued prior to completion
    - Reasons for discontinuation prior to completion will also be summarized descriptively

In addition, there will also be a listing of all discontinued subjects, which will provide the clinical trial center and the specific reason for discontinuation.

8.1.2 Protocol Deviations

The major protocol deviations occurred during the clinical trial will be summarized descriptively according to the following categories:

- Informed consent not properly attained
- Developed withdrawal criteria during the study but not withdrawn
- Received excluded concomitant medication
- Did not meet Inclusion/ Exclusion criteria but entered into the study

Additionally a by-subject listing of all deviations will also be prepared.

8.1.3 Demographics and Other Baseline Characteristics

Demographics (age, race, gender, ethnicity), height, weight will be listed and summarized descriptively. See Section 7.1 for baseline definition.

Medical history findings will be provided as by-subject listings.

8.1.4 Prior and Concomitant Medications

All prior and concomitant medications recorded in the case report form will be using the most recent version of WHO Drug dictionary. Descriptive summaries will be prepared using the coded

term. All prior and concomitant medications recorded in the case report form will be listed and summarized.

8.1.5 Study Drug Administration

All available study drug administration data will be listed and summarized.

8.2 Analysis Primary Outcome Measure

8.2.1 Maximum Tolerated Dose (MTD) by evaluation of dose-limiting toxicities (DLTs) of leronlimab (PRO 140) when combined with carboplatin AUC5

The MTD will be summarized descriptively. The proportion of subjects at the different MTD levels and those who were able to tolerate the highest dose of leronlimab will be summarized descriptively.

8.2.2 Progression free survival (PFS) defined as time in months from the date of first study treatment to the date of disease progression or death from any cause, whichever comes first.

PFS will be calculated from the date of initial dose to the date of objective disease progression or death due to any cause, whichever occurs earlier. If patients discontinued treatment due to toxicity, withdrew consent without disease progression or death, PFS will be censored at the date of the last evaluable tumor assessment. A patient with no evaluable tumor assessments or who drop out before first follow-up period will be censored at the date of informed consent. If two or more consecutively scheduled tumor assessments have no data (not evaluable due to incomplete assessment, not assessed, or missing) and are followed by a PD assessment or death, the PFS will be censored at the last evaluable tumor assessment date prior to the assessments with no data. Patients will be explicitly censored for PFS at last adequate tumor assessment prior to initiation of new anticancer treatment or radiation.

Patients who are off-treatment without objective PD and getting the subsequent new anticancer therapy before the data cut-off then PFS will be censored at the last adequate tumor assessment before the new anticancer treatment start, regardless of whether there was a PD or death after the start of the new anticancer treatment.

Progression free survival (PFS) will be estimated using Kaplan-Meier curves, and the median PFS will be read from this curve.

8.3 Analysis of Secondary Outcome Measures

8.3.1 PFS according to RECIST v1.1 in participants with Detectable Programmed Death-Ligand 1 (PD-L1)

PFS according to RECIST v1.1 in participants with Detectable Programmed Death-Ligand 1 (PD-L1) will be calculated using Kaplan-Meier curves, and the median PFS will be read from this curve.

Note: The PD-L1 expression testing will be performed at baseline. Breast tissue (primary or metastatic site) collected to analyze for the presence of CCR5 at pre-screening will additionally be used for evaluating PD-L1 expression levels.

8.3.2 Overall response rate (ORR) and clinical benefit rate (CBR) in subjects with CCR5+ mTNBC treated with leronlimab (PRO 140) and carboplatin

Overall response rate (ORR) and clinical benefit rate (CBR) in subjects with CCR5+ mTNBC treated with leronlimab (PRO 140) and carboplatin will be calculated using proportions and 95% confidence intervals.

Note: Overall response rate defined as the proportion of patients who achieve an overall response of complete response or partial response in the total number of evaluable patients, assessed by RECIST v1.1. Clinical benefit rate is defined as the proportion of patients who achieve an overall response of complete response or partial response or stable disease in the total number of evaluable patients, assessed by RECIST v1.1. Imaging scans to be done at the end of 2 cycles (i.e., every 6 weeks) for the first 6 cycles (18 weeks) and at the end of 3 cycles (i.e., every 9 weeks) thereafter.

8.3.3 Time to new metastases (TTNM)

Time to new metastases (TTNM) will be calculated using the formula in Section 7.9.3 and summarized descriptively. Kaplan-Meier analysis will be used to depict the median time (days) to new metastases.

Note: Recorded time from baseline metastatic disease (at time of enrollment) to the time of development of new metastasis in different site. New metastases in same site will be also recorded.

8.3.4 The change from baseline in circulating tumor cells (CTC) level in the peripheral blood

The change from baseline in circulating tumor cells (CTC) level in the peripheral blood will be calculated for each subject at each timepoint and summarized descriptively.

Note: Reported unit of measure will be the number of CTCs/milliliter. CTCs enumeration will be performed at baseline and at the time of response assessment. Fraction of baseline positive and change from ≥5 CTCs will be recorded and reported.

8.3.5 Overall survival defined as time in months from the date of first study treatment to the date of death

Overall survival defined as time in months from the date of first study treatment to the date of death will be presented using proportions and 95% confidence intervals.

Note: Patients will be followed from the start of treatment until 2 years post-treatment or death, whichever occurs first, and average survival time will be measured.

8.3.6 Exploratory Outcome Measures

8.3.6.1 Measure immune biomarkers (PD-L1) in CTCs, metastatic tissue and immune cells such as CAMLs and correlate with therapeutic benefit (PFS)

Immune biomarkers (PD-L1) in CTCs, metastatic tissue and immune cells such as CAMLs will be related to PFS using Cox regression.

8.3.6.2 Correlation between CCR5 expression (CTCs, CAMLs) and PD- L1 expression

CCR5 expression (CTCs, CAMLs) and PD- L1 expression will be correlated using logistic regression.

8.4 Analysis of Safety Data

All safety analyses will be conducted using the Safety population. All data collected will be summarized according to the variable type. No inferential statistics are planned.

8.4.1 Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent version of MedDRA dictionary.

TEAE are defined as adverse events with onset date on or after the first treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

a) Overall (*i.e.,* regardless of severity or relationship to treatment)
b) By severity grade
c) By relationship to clinical trial treatment

Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

AEs leading to premature discontinuation of clinical trial treatment and Serious Adverse Events (SAEs) will also be summarized by treatment group and relationship.

All adverse events recorded in the eCRF will be presented as by-subject listings.

8.4.2 Injection Site Reaction Assessment

Injection Site Reaction Assessment will be presented as by-subject listing and summarized.

All data from the injection site reaction assessments of the repeated subcutaneous administration of PRO 140 will be descriptively summarized.

8.4.2.1 Injection Site Reactions per DAIDS AE Grading

Local injection-site reactions are assessed for each injection including Pain, Erythema¸ Pruritis, Bleeding and Absorption of drug.

Each injection site reaction is monitored per protocol-defined severity criteria developed in align with the guidelines of (Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [DAIDS AE Grading Table])

Table 8-1: Injection-site Reactions, DAIDS Grading

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Injection-site pain	Pain without touching or pain when area is touched: no or minimal limitation of use of limb	Pain without touching or pain when area is touched limiting use of limb OR causing greater than minimal interference with usual social and functional activities	Pain without touching or pain when area is touched causing inability to perform usual social and functional activities	Pain without touching or pain when area is touched causing inability to perform basic self-care function OR hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Characterization of the injection site, if not normal	Erythema OR induration of 5x5 cm - 9x9 cm (or 25 cm2-81 cm2)	Erythema OR induration OR Edema > 9 cm any diameter (or > 81 cm2)	Ulceration OR secondary infection OR Phlebitis or Sterile abscess OR drainage	Necrosis (involving dermis and deeper tissue)
Pruritus associated with injection	Itching localized to injection site AND relieved spontaneously or < 48 hours of treatment	Itching beyond the injection site but not generalized OR itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social and functional activities	N/A
Bleeding	Initial bleed that does not exceed bandage and spontaneously stops	Bleeding that exceeds bandage and spontaneously stops	Continued bleeding that requires change of dressing and alternative injection site	N/A

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Absorption of drug	Minor elevation of skin at injection site but no leakage of injection material	Leakage at injection site ceases with decrease in injection rate	Leakage at injection site that does not cease with decrease in injection rate	

The grading for all subjects and parameters will be listed. The number and percentage of patients with worst reported DAIDS grade will be summarized regardless of the location of injection (i.e., left or right side) in the abdomen. Each patient will be counted only for the worst grade observed.

In addition, time to onset of the first worst case injection site reaction will be summarized.

Time to onset of worst grade will be summarized for each local injection reaction parameter listed above using Kaplan-Meier method. Median time to onset and 95% C.I will be summarized. In addition, Kaplan-Meier plots will be generated.

8.4.2.2 *Systemic manifestations (e.g., hypotension, fever, difficulty breathing) within the post-administration monitoring period*

This will be assessed from the vital signs data using the pre and post assessment:

- Hypotension – if there is a reduction in SBP of >= 20 mmHg or reduction in DBP of >= 10 mmHg or if post treatment SBP is >= 90mmHg or DBP is <=60mmHg
- Fever – if post treatment temperature is > 40^0C
- Difficulty breathing – if increase in Respiratory Rate is > 30%

The subjects with above systemic manifestations will be listed. Shift table for Fever will be presented with counts and percentages of subjects for shift (change) from pre-treatment at T1 to post-treatment at T1. Percentage of subjects with Hypotension or Difficulty breathing post treatment will be summarized.

8.4.2.3 *Local and Systemic reactions, Hypersensitivity and Anaphylaxis reaction to Injection*

All adverse events reported as related to sub-cutaneous injection of study treatment will be presented as by-subject listing and summarized by System Organ Class (SOC) and Preferred term (PT). The list of SOC and PT to be used for this purpose are presented in Section 10.1.

8.4.2.4 Risk factors for injection site reactions

The available data will be reviewed to identify any potential risk factors and risk groups for injection site reactions.

The risk factors more commonly include the skin's response to the needle or the medicine. An allergic reaction to the medicine or an infection at the injection site.

Possible risk factors that can be analyzed include:

- Dose
- Frequency of Injection
- History of injection site reactions
- Patient demographics

8.4.2.5 *Impact of injection site reactions on patient outcomes (e.g., leronlimab discontinuation, additional treatment required or preventative measures)*

Any impact of injection site reactions on patient outcomes (e.g., leronlimab interruption, discontinuation, additional treatment or preventative measures required) will be presented

8.4.3 Clinical Laboratory Evaluations

All results of laboratory evaluations will be presented as by-subject listings.

8.4.3.1 Laboratory Values over Time

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented by treatment group and time point. Data will be summarized as appropriate for the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.4.3.2 Individual Patient Changes

Laboratory data will be classified into grades according to DAIDS toxicity grading. A severity grade of 0 will be assigned when the value is within normal limits.

The following summaries will be produced for the hematology and biochemistry laboratory data (by laboratory parameter):

- Shift tables using DAIDS grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with DAIDS grades
- Shift tables using Low/High/Normal relative to the laboratory reference ranges to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters without DAIDS grades

8.4.3.3 Individual Subject Changes on Interpretation

Shift tables will be presented for the investigator lab interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, by treatment group, for shift (change) from baseline, using the normal ranges.

8.4.3.4 Individual Clinically Significant Abnormalities

Clinically significant laboratory abnormalities (i.e., those laboratory abnormalities recorded as AEs) will be listed.

8.4.4 Vital Signs

Vital sign assessments are performed in order to characterize basic body function. The parameters collected in this study are: systolic BP (mmHg), diastolic BP (mmHg), temperature (0C), heart rate (bpm), respiratory rate (rpm).

8.4.4.1 Clinically notable elevated values

- Systolic BP: ≥ 160 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 100 mmHg and an increase ≥ 15 mmHg from baseline.
- Body temperature: ≥ 39.1°C
- Heart rate: ≥ 120 bpm with increase from baseline of ≥15 bpm
- Respiration rate: ≥ 24 breaths per minute with increase from baseline of ≥ 6 breaths per

minute

8.4.4.2 Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Body temperature: ≤ 35°C
- Heart rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm
- Respiration rate: < 8 breaths per minute with decrease from baseline of ≥ 6 breaths per minute

Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e. both elevated and below normal values) will be summarized by treatment group.

8.4.5 Electrocardiogram (ECGs)

The ECG parameters include: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec).

The number and percentage of patients having notable ECG interval values and newly occurring qualitative ECG abnormalities will be summarized by treatment group.

The following notable ECG interval values for each parameter will be presented as by-subject listing. Number and percentage of subjects with at least one occurrence of the below notable ECG changes will be summarized.

QT and QTc:

(1) New >450 msec

(2) New >480 msec

(3) New >500 msec

(4) Increase from baseline >30 msec

(5) Increase from baseline >60 msec

Shift tables will also be presented for the categories of QT results (<=450, >450-480, >480-500, >500) with counts and percentages of subjects, for shift (change) from baseline.

PR:

(1) An increase >25% from baseline and PR >200 msec at any post-baseline assessment

QRS:

(1) An increase >25% from baseline and QRS >110 msec at any post-baseline assessment

Ventricular rate :

(1) A decrease >25% from baseline and HR <50 bpm at any post-baseline assessment

(2) An increase >25% from baseline and HR >100 bpm at any post-baseline assessment

In addition, individual subject changes will be identified through shift tables. Shift tables will be presented for the investigator ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, for shift (change) from baseline.

8.4.6 Physical Examination

8.4.6.1 Physical Examination Values over Time

Summary of the number and percentage of subjects will be presented for the investigator interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) by treatment group and time point.

8.4.6.2 Individual Patient Changes

Individual subject Physical Examination findings will be identified through shift tables. Shift tables will be presented for the investigator interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, by treatment group, for shift from baseline.

8.4.6.3 Clinically Significant Abnormalities

A by-subject listing of treatment-emergent clinically significant Physical Examination, by treatment group, will be prepared.

8.4.7 Serum Pregnancy Test

All the results for serum pregnancy test will be presented as a by-subject listing.

8.4.8 Urine Pregnancy Test

All data from Urine Pregnancy test will be presented as a by-subject listing.

8.4.9 ECOG Performance Status

All ECOG Performance Status findings will be listed and/or summarized by treatment group.

8.4.10 Pregnancy Test

All the results for pregnancy test will be presented as by-subject listing.

8.4.11 Injection Site Pain Assessment

Injection Site Pain Assessment will be presented as by-subject listing and summarized.

9. APPENDIX 1

FIGURE 9-1: SCHEDULE OF ASSESSMENTS

Tests and Assessments	Screening Period		Treatment Period									Follow-up Period	
			Treatment Cycle 1 (21 days)			Treatment Cycle 2 (21 days)			Additional Treatment Cycles				
Visit	Pre-Screening Visit [1]	Screening Visit	C1D1	C1D8	C1D15	C2D1	C2D8	C2D15	CXD1	CXD8	CXD15	EOT	Survival Follow-ups
Day(s)			Day 1	Day 8	Day 15	Day 22	Day 29	Day 36					
Window			Within 28 Days from Screening visit	7 (±1) Days from C1D1 visit	7 (±1) Days from C1D8 visit	7 (±1) Days from C1D15visit	7 (±1) Days from C2D1 visit	7 (±1) Days from C2D8 visit	7 (±1) Days from last visit	7 (±1) Days from last visit	7 (±1) Days from last visit	30 Days (±3) after last treatment visit	Every 3 months [20]
Informed Consent [2]	X	X											
Demographics		X											
Medical and Medication History [3]	X	X											
Vital Signs [4]		X	X	X	X	X	X	X	X	X	X	X	
Height and Weight		X	X[5]			X[5]			X[5]				
Physical Exam		X	X	X[6]	X[6]	X	X[6]	X[6]	X	X[6]	X[6]	X	
ECOG Performance Status		X	X			X			X			X	
Electrocardiogram, 12-lead [7]		X	X									X	
Toxicity assessment (post treatment)			X			X			X			X[21]	X[22]
Tumor Imaging Assessment [8]		X							X				X[22]
Complete Blood Count [9]		X	X			X			X			X	
Biochemistry [10]		X	X			X			X			X	
Urinalysis [11]		X	X			X			X			X	
Serum Pregnancy test [12]		X											
Urine Pregnancy test [12]			X			X			X				
Eligibility Assessment	X	X	X										
Enrollment / Cohort Assignment			X										
Blood sample collection for CTC and PDL-1 Analysis [13]			X			X			X			X	
Blood sample collection for CTC and			X			X			X			X	

Tests and Assessments	Screening Period		Treatment Period									Follow-up Period	
			Treatment Cycle 1 (21 days)			Treatment Cycle 2 (21 days)			Additional Treatment Cycles				
Visit	Pre-Screening Visit [1]	Screening Visit	C1D1	C1D8	C1D15	C2D1	C2D8	C2D15	CXD1	CXD8	CXD15	EOT	Survival Follow-ups
Day(s)			Day 1	Day 8	Day 15	Day 22	Day 29	Day 36					
Window			Within 28 Days from Screening visit	7 (±1) Days from C1D1 visit	7 (±1) Days from C1D8 visit	7 (±1) Days from C1D15visit	7 (±1) Days from C2D1 visit	7 (±1) Days from C2D8 visit	7 (±1) Days from last visit	7 (±1) Days from last visit	7 (±1) Days from last visit	30 Days (±3) after last treatment visit	Every 3 months [20]
CAMLs Analysis [14]													
Tissue for CCR5 (archival or fresh biopsy)	X[15]												
PRO 140 administration [16]			X	X	X	X	X	X	X	X	X		
Carboplatin administration [17]			X			X			X				
Post Injection Site Evaluation by Investigator [18]			X	X	X	X	X	X	X	X	X		
Injection Site Pain Assessment (VAS) [19]				X	X	X	X	X	X	X	X		
Survival status												X	X[20]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X[23]
Adverse Events			X	X	X	X	X	X	X	X	X	X	

Footnotes

[1] A separate Informed Consent Form (ICF) will be used for the pre-screening. The pre-screening period is designed for evaluation of histologically confirmed diagnosis of TN MBC (documented by HER-2 negative, ER<1%, PR<1%) and CCR5 positive status by Immunohistochemistry (IHC) assay. This assay will be performed in archival tissue from previous biopsy specimens. If archival tissue is not available then, fresh core or excisional biopsy will be done. If patient qualifies, then they will undergo full screening.

[2] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.

[3] A complete review of the subject's past medical history, past surgeries, and current therapies (medications and non-medications) will be undertaken by the Investigator to check that all inclusion and no exclusion criteria have been met.

[4] Vital signs include blood pressure, heart rate, respiration rate, and temperature.

[5] Weight only

[6] Symptom-directed physical examination

[7] A 12-lead EKG will be repeated during the study only if clinically indicated and at the discretion of the treating physician.

[8] Scans are to be done at the end of 2 cycles (prior to cycle 3) for the first 13 months and at end of 3 cycles (9 weeks) thereafter, and at End of Treatment (EOT) visit by CT, PET/CT or MRI with contrast (per treating investigator's discretion) using the same method as at baseline. Tumor measurements will be done using RECIST1.1. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 6 weeks after the criteria for response are first met. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

[9] Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC) with total and differential count, absolute lymphocyte count, absolute neutrophil count (ANC) and platelets.

[10] Serum Biochemistry will include:
Hepatic function indicators: total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin and total protein.
Renal function indicators: blood urea nitrogen (BUN), creatinine
Electrolytes: sodium, potassium, chloride, calcium and bicarbonate
Other: glucose (random)

[11] Urine samples will be tested for pH, appearance, color, specific gravity, turbidity, ketones, bilirubin, blood, glucose, protein, nitrites, urobilinogen, and leukocyte esterases. Microscopic exam includes bacteria, cast, crystals, epithelial cells, RBC and WBC.

[12] Only performed on women of childbearing potential

[13] Blood sample collection for CTC and PDL-1 analysis to be taken prior to the treatment administration at baseline (C1D1), on Day 1 (CXD1) of each subsequent cycle, and at the end of treatment (EOT).

[14] Blood sample collection for CTC and CAMLs analysis to be taken prior to treatment administration at baseline (C1D1), on Day 1 (CXD1) of each subsequent cycle, and at the end of treatment (EOT).

[15] Archival breast tissue (primary or metastatic site) will be collected from all patients at the pre-screening period and analyzed for presence of CCR5. Note: If no archival tissue is available, fresh biopsy to be done of the primary or metastatic site within 42 days (6 weeks) prior to initiation of treatment on Day 1.

[16] PRO 140 is administered as subcutaneous injection in the abdomen weekly. A total of 350mg or 525 mg or 700mg (175 mg/mL) is delivered as two injections on opposite sides of the abdomen. The 350mg dose will be delivered as two injections of 1 mL each, 525mg dose will be delivered as two injections of 1.5 mL each and 700mg dose will be delivered as two injections of 2 mL each.

[17] Carboplatin will be IV infused at AUC 5 on D1 of each cycle, every 3 weeks

[18] Injection Site Reaction Assessment as assessed by Investigator (or designee)

[19] Subject-perceived injection site pain (average pain since last treatment) will be assessed using the Pain Visual Analog Scale (VAS) prior to each study treatment administration

[20] Subjects will be followed up by clinic visits or phone call or another method of contact, for survival status every 3 months (±1 month) for 2 years after treatment discontinuation or until death, whichever occurs first

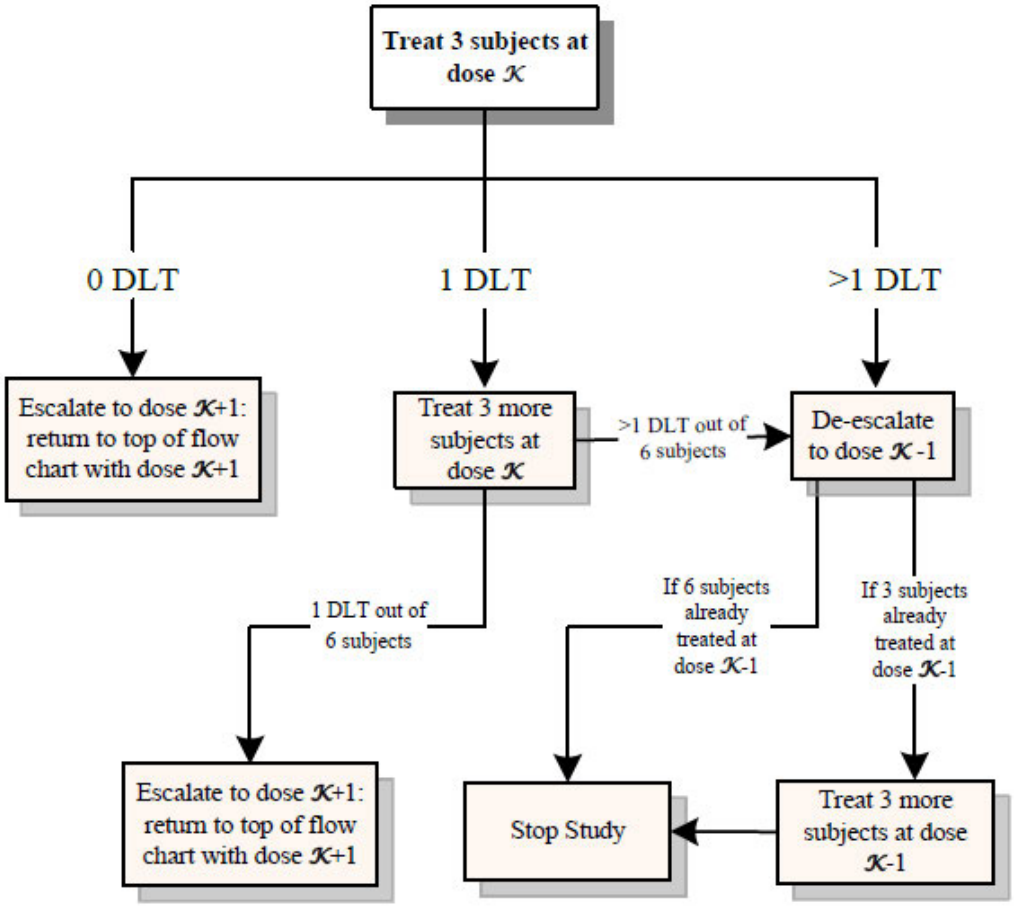
[21] All subjects will be followed for adverse events for 30 days after last dose of PRO 140 and carboplatin, or until the subject starts a new treatment, whichever occurs first.

[22] Subjects who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event (i.e. the grade is not changing). If a subject stops treatment due to unacceptable adverse event(s) but has not demonstrated disease progression, then the subject will be followed with imaging studies every 9 weeks until the time of progression radiographically according to RECIST 1.1 criteria. In the event that a radiographic response is detected, then this event will be included as a response in the final analysis, and the time of progression used in calculation of the survival analysis.

[23] Limited to all subsequent anti-cancer treatments.

10. APPENDIX 2

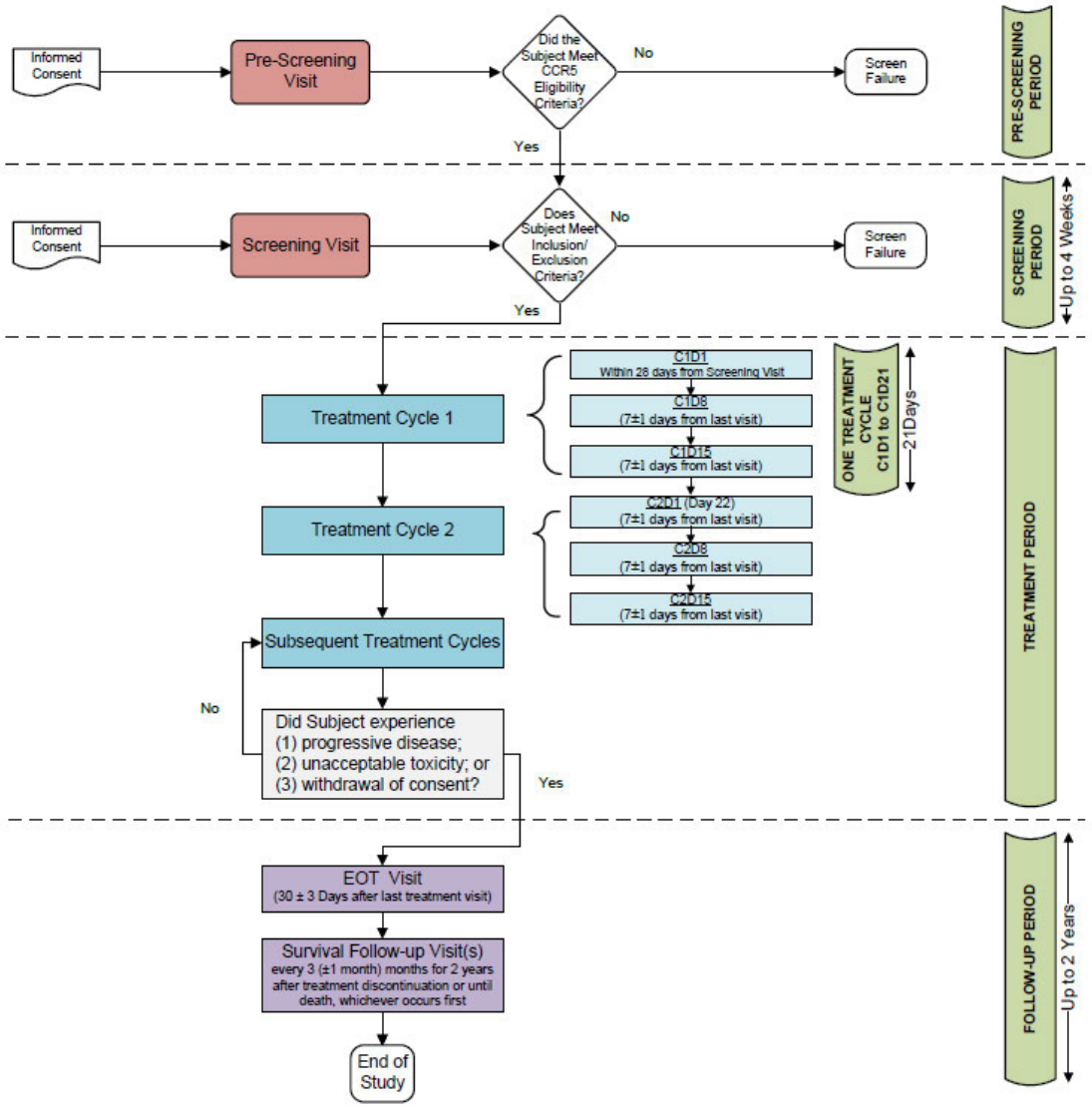
Figure 3-2: 3+3 Study Design



Note: A standard "3 +3" dose escalation design starting at dose $\mathcal{K}$. The maximum tolerated dose (MTD) is the highest dose at which 0 or 1 dose-limiting toxicities (DLTs) are observed in six subjects. If de-escalation occurs at the first dose level, the study is discontinued.

11. APPENDIX 3

Figure 4-1: Study Flow Diagram



12. APPENDIX 4

12.1 Planned By-Subject Listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

ELIGIBILITY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)

DEMOGRAPHICS, POPULATION, AND BASELINE CHARACTERISTICS (LISTINGS 16.2.4.X)

DRUG COMPLIANCE (LISTINGS 16.2.5.X)

EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT DATA (LISTINGS 16.2.7.X)

SAFETY DATA (LISTINGS 16.2.8.1.X)

OTHER SAFETY DATA (LISTINGS 16.2.8.2.X)

OTHER LISTINGS (LISTINGS 16.2.8.3.X)

12.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS
POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS
CONCOMITANT MEDICATION USAGE
EFFICACY SUMMARIES
SAFETY SUMMARIES
- ADVERSE EVENT SUMMARIES
- SERIOUS ADVERSE EVENTS
- LABORATORY
- VITAL SIGNS AND PE
- OTHER SAFETY

13. REFERENCES

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2. The Royal Statistical Society: Code of Conduct (2014).
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4. E9(R1) Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 2017
5. Guideline for the Format and Content of the Clinical and Statistical Section of an Application, 1988.
6. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3(R1)), July 2013.