CYTODYN

Statistical Analysis Plan Cover Page

Document Title: Statistical Analysis Plan for Protocol CD07_TNBC_Compassionate Use

Protocol Number: CD07_TNBC_CompassionateUse

Protocol Title: A Compassionate Use Study of Leronlimab (PRO 140) plus Treatment of Physician's Choice in Patients with CCR5+ Metastatic Triple-Negative Breast Cancer (mTNBC)

Version: 1.0

Document Date: 22-June-2020

NCT Number: NCT04313075

STATISTICAL ANALYSIS PLAN
FOR PROTOCOL CD07_TNBC_COMPASSIONATEUSE

Sponsor:	**CytoDyn, Inc.** 1111 Main Street, Suite 660 Vancouver, Washington 98660	(360) 980-8524-Work (360) 980-8549-Fax www.cytodyn.com
Protocol Number:	CD07_TNBC_ CompassionateUse	
Protocol Title:	A Compassionate Use Study of Leronlimab (PRO 140) in combination with Treatment of Physician's Choice in Patients with CCR5+ Metastatic Triple Negative Breast Cancer (mTNBC)	
Protocol Date / Version:	May 14, 2020/Version 4.0	

SAP Author:	[redacted]	Telephone:	[redacted]
		Facsimile:	[redacted]

Plan Version:	SAP – Version 0.1
Plan Date:	22 June 2020

Protocol Number:	CD07_TNBC_ Compassionate Use
Protocol Version:	May 14, 2020/Version 4.0
Protocol Name:	A Compassionate Use Study of Leronlimab (PRO 140) in combination with Treatment of Physician's Choice in Patients with CCR5+ Metastatic Triple Negative Breast Cancer (mTNBC)
Sponsor:	CytoDyn, Inc. 1111 Main Street, Suite 660 Vancouver, Washington 98660
Prepared by:	[redacted]
SAP Version:	SAP – Version 0.1
SAP Date:	22 June 2020

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

Statistician, [redacted]	Date
CytoDyn, Inc.	Date

TABLE OF CONTENTS

ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CRF	Case Report Form
CS	Clinically Significant
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
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
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection Site Reactions
IV	Intravenous
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PI	Principal Investigator
PP	Per Protocol
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease
SLD	Sum of the Longest Diameters
SOP	Standard Operating Procedure
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event
TNBC	Triple Negative Breast Cancer
TTNM	Time to New Metastasis
VAS	Visual Analog Scale
VF	Virologic Failure

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for the clinical trial protocol CD07_TNBC_ CompassionateUse , 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 Version 4.0/May 14, 2020
- 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

This is a single arm, compassionate use study with 30 patients for leronlimab (PRO 140) combined with a treatment of physician's choice (TPC) in patients with CCR5+ mTNBC.

Leronlimab (PRO 140) will be administered subcutaneously as weekly dose of 350 mg until disease progression or intolerable toxicity. Treatment of Physician's Choice (TPC) is defined as one of the following single-agent chemotherapy drugs administrated according to local practice: eribulin, gemcitabine, capecitabine, paclitaxel, nab-paclitaxel, vinorelbine, ixabepilone, or carboplatin. The selected treatment should be administered as per the dosing schedule included on the package insert.

In this study, patients will be evaluated for tumor response approximately every 3 months or according to institution's standard practice 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 Figure 4-1.

(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 (prior imaging assessment within the last 3 months of the Screening Visit is acceptable), 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.

Leronlimab (PRO 140) will be administered subcutaneously weekly in combination with a treatment of physician's choice. The study treatment will be administered by a licensed medical professional at clinic site or self-administered by subjects at home.

Note: All initial leronlimab (PRO 140) SC weekly injections must be administered at clinic. The remaining study treatment injections may be self-administered by subjects at home after proper training by a healthcare professional.

Subjects will be allowed to continue weekly treatment 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)). 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

- 350 mg leronlimab (PRO 140)

2.2.2 Duration of treatment

- **Pre-Screening Period**: N/A (no pre-defined window period)
- **Screening Period**: Up to 4 weeks
- **Treatment Period:** Weekly treatment visits starting within 4 weeks of the screening period.

  *Subsequent Treatment Visits: Subjects will be eligible for continuing treatment beyond first week in absence of disease progression or unacceptable toxicity or withdrawal of consent
- **Follow-Up Period:** 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)

Primary Objectives:

The primary objective of this study is to assess anti-tumor activity of Leronlimab (PRO 140) in combination with Treatment of Physician's Choice in the treatment of patients with CCR5+ Metastatic Triple Negative Breast Cancer (mTNBC) as part of a defined treatment protocol.

Secondary Objective:

The secondary objective of this study is to collect further safety, tolerability and efficacy data. To evaluate correlative studies for better treatment selection in future validation studies

2.4 Study Outcomes Measures:

2.4.1 Efficacy Outcome Measures

- 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) 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.

- 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) combined with a treatment of physician's choice.

  Note: Overall response rate is 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 approximately every 3 months or according to institution's standard practice.

- 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.

2.4.2 **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.

2.4.3 **Safety Outcome Measure**

- 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) in subjects with CCR5+ mTNBC.

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

- Laboratory data changes from baseline to subsequent scheduled visits
- Changes in physical examinations from baseline to subsequent scheduled visits
- Changes in vital signs from baseline to subsequent scheduled visits.
- Changes in Eastern Cooperative Oncology Group (ECOG) performance status from baseline to subsequent scheduled visits.
- Changes of electrocardiogram (ECG) results from baseline to subsequent scheduled visits.

3. SAMPLE SIZE DETERMINATION

This is a multicenter study and up to 30 subjects will be enrolled in this study. The sample size for is based on clinical judgment. No statistical power calculation is used to establish the sample size.

4. INTERIM ANALYSIS

No Interim Analysis (IA) will be performed for efficacy.

5. HYPOTHESIS TO BE TESTED

There is no formal hypothesis testing for this study.

6. ANALYSIS POPULATIONS

6.1.1 Evaluable Population

The Evaluable 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. This population will be used for the analysis of efficacy parameters or measurements.

6.1.2 Per Protocol (PP) population

The Per Protocol (PP) population is defined as the set of subjects who meet the Evaluable Population requirements and were not associated with any major protocol violations. This population will be identified before the database lock.

The PP analysis of primary and secondary endpoints 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.

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

For efficacy analyses, the baseline values will be used as covariates in the analysis models. Other important prognostic factors will be specified in the SAP for the 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 collected during this study will be presented in subject data listings. All statistical analyses will be performed using SAS® for Windows, version 9.4 or later.

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 numbers of subjects screened
- The numbers of subjects enrolled
- The number of subjects who completed the study
- The number of subjects who completed treatment
- The number of subjects who discontinued prior to completion
    - Reasons for discontinuation prior to completion will also be summarized descriptively

In addition, disposition and reason for study discontinuation will also be provided as a by-subject listing

8.1.2 **Protocol Deviations**

The deviations occurring during the clinical trial will be summarized descriptively according to the following categories:

- Informed consent not properly attained
- Did not meet Inclusion/Exclusion criteria but entered into study
- Developed withdrawal criteria during the study but not withdrawn
- Procedure performed out of window
- Received excluded concomitant medication
- Missed procedure or visit

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/or summarized.

8.2 Analysis of Efficacy Outcome Measures

8.2.1 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 calculated using Kaplan-Meier curves, and the median PFS will be read from this curve.

8.2.2 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.

8.2.3 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) combined with a treatment of physician's choice.

Overall response rate (ORR) and clinical benefit rate (CBR) in subjects with CCR5+ mTNBC treated with leronlimab (PRO 140) combined with a treatment of physician's choice will be calculated using proportions and 95% confidence intervals.

Note: Overall response rate is 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 approximately every 3 months or according to institution's standard practice.

8.2.4 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.

8.2.5 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 time point 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.

8.2.6 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 calculated using proportions and 95% confidence intervals.

8.3 Exploratory Outcome Measures

8.3.1 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.

8.3.2 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 coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by study phase, 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 (mild, moderate, severe, or life threatening for SAEs)

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 Clinical Laboratory Evaluations

Clinical laboratory evaluations (Biochemistry, Hematology, Urinalysis and CCR5-IHC Assay) will be listed and/or summarized, as follows.

*8.4.2.1 **Laboratory Values over Time***

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

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

*8.4.2.2 **Individual Subject Changes (Shift Tables)***

Individual subject changes will be identified through shift tables. Shift tables will be presented for each laboratory parameter with counts and percentages of subjects, by treatment group and time point, for shift (change) from baseline, using the normal ranges from the laboratory.

*8.4.2.3 **Individual Clinically Significant Abnormalities***

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

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

8.4.3 **Vital Signs**

Tabulations of raw data and change from baseline values will be presented by time point for each vital sign parameter.

Tabulations will include the number of observations, mean, standard deviation, median, and minimum and maximum values. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.4.4 **Electrocardiogram (ECGs)**

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

*8.4.4.1 **ECG Values over Time***

Descriptive statistics of raw data and change from baseline values for each ECG measurement will be presented by treatment group. For change from baseline summaries, subjects with an undefined change from baseline, because of missing baseline data, will be excluded.

*8.4.4.2 **Individual Subject Changes (Shift Tables)***

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, by treatment group, for shift (change) from baseline, using the normal ranges.

8.4.4.3 ***Clinically Significant Abnormalities***

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

8.4.5 **Physical Examination**

All physical examination findings will be listed and/or summarized by Treatment group.

8.4.6 **Serum Pregnancy Test**

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

8.4.7 **Urine Pregnancy Test**

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

8.4.8 **ECOG Performance Status**

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

8.4.9 **Notification and Outcome description from Pregnancy**

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

8.4.10 **Injection Site Pain Assessment**

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

8.4.11 **Injection Site Reaction Assessment**

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

8. APPENDIX 1

FIGURE 8-1: SCHEDULE OF ASSESSMENTS

Tests and Assessments	Screening Period		Treatment Period														Follow-up Period	
Visit	Pre-Screening Visit [1]	Screening Visit	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	TX	Add. Rx Visits [26]	EOT	Survival Follow-ups
Day(s)			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week Tx			
Window			±3 days since last treatment															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	X	X	X	X		X	
Height and Weight		X	X[5]			X[5]			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	X[6]	X[6]	X	X[6]		X	
ECOG Performance Status		X	X			X			X			X			X			X	
Electrocardiogram, 12-lead [7]		X	X															X	
Toxicity assessment (post treatment)			X			X			X			X			X			X[21]	X[22]
Tumor Imaging Assessment [8]		X																	X[22]
Complete Blood Count [9]		X	X[24]			X[24]			X[24]			X[24]			X[24]			X	
Biochemistry [10]		X	X[24			X[24			X[24			X[24			X[24			X	
Urinalysis [11]		X	X			X			X									X	
Serum Pregnancy test [12]		X																	
Urine Pregnancy test [12]			X			X			X			X			X				
Eligibility Assessment	X	X	X																

Tests and Assessments	Screening Period		Treatment Period														Follow-up Period	
Visit	Pre-Screening Visit [1]	Screening Visit	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	TX	Add. Rx Visits [26]	EOT	Survival Follow-ups
Day(s)			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week Tx			
Window			±3 days since last treatment															30 Days (±3) after last treatment visit	Every 3 months [20]
Enrollment / Cohort Assignment			X																
Blood sample collection for CTC and PDL-1 Analysis [13]			X			X			X			X			X			X	
Blood sample collection for CTC and CAMLs Analysis [14]			X			X			X			X			X			X	
Tissue for CCR5 (archival or fresh biopsy)	X[15]																		
Tissue for PD-L1 expression level	X[16]																		
leronlimab (PRO 140) administration [17]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Post Injection Site Evaluation by Investigator [18]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Injection Site Pain Assessment (VAS) [19]				X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatment of Physician's Choice [25]			X																
Survival status																		X	X[19]
Concomitant medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[22] [22]
Adverse Events				X	X	X	X	X	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 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] Informed consent must be obtained prior to patient participation in any protocol-related activities that are not part of routine care.

A complete review of the subject's past medical history (including all prior anti-tumoral therapy related to breast cancer), 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 will be measured at clinic visit.

[5] Weight only

[6] Symptom-directed physical examination at clinic visits

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

[8] Prior tumor imaging assessment within the last 3 months of the Screening Visit is acceptable. During the Treatment Phase, scans are to be done approximately every 3 months or according to institution's standard practice 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. 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, direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/SGOT, alanine aminotransferase (ALT)/SGPT, 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 CTCs PD-L1/CCR5 analysis to be taken prior to the treatment administration at T1 and every 3 weeks thereafter, and at the end of treatment (EOT).

[14] Blood sample collection for CTC and CAMLs analysis to be taken prior to treatment administration at T1 and every 3 weeks thereafter, 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.

[16] Breast tissue (primary or metastatic site) collected to analyze for the presence of CCR5 will additionally be used for evaluating PD-L1 expression levels. The PD-L1 expression testing will be performed at the reference laboratory using the formalin-fixed, paraffin-embedded (FFPE) tissue block or slides.

[17] Leronlimab (PRO 140) is administered as subcutaneous injection in the abdomen weekly. A total of 350 mg (175 mg/mL) is delivered as two injections of 1 mL each on opposite sides of the abdomen.

[18] Injection Site Reaction Assessment as assessed by Investigator (or designee) at the clinic visits. Injection Site Reaction Assessment will not be applicable if leronlimab (PRO 140) is self-administered by subjects at home.

[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 which evaluates average pain since last treatment. Injection Site Pain Assessment will not be applicable if leronlimab (PRO 140) is self-administered by subjects at home.

[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 leronlimab (PRO 140), 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 v1.1 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.

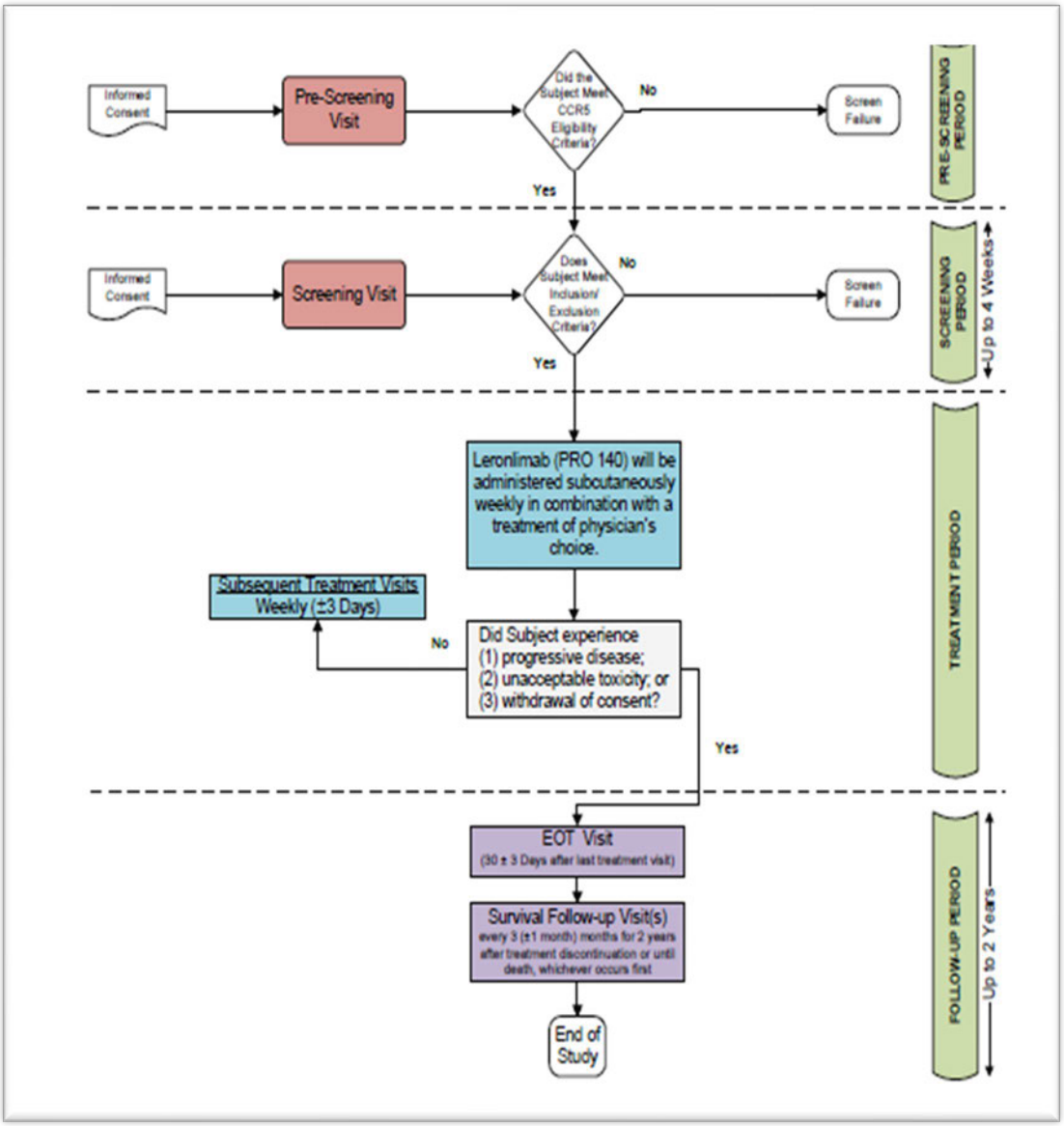
[24] Can be performed within 3 days prior to each treatment visit.

[25] Subjects will receive treatment assigned by the physician on the regimen's established schedule. See Section 7.17

[26] Subjects can continue to receive treatment until one of the following occurs: progressive disease, unacceptable toxicity, or withdrawal of consent

9. APPENDIX 2

FIGURE-9-1 STUDY FLOW DIAGRAM



10. APPENDIX 4

10.1 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)

10.2 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

11. REFERENCES

1. ASA. (2016) Ethical Guidelines for Statistical Practice.
2. The Royal Statistical Society: Code of Conduct (2014).
3. E8 General Considerations for Clinical Trials, ICH Guidance, Federal Register, 1997.
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.