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Statistical Analysis Plan Cover Page

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Protocol Number: CD09_Basket

Protocol Title: Basket Study of Leronlimab (PRO 140) in Patients with CCR5+ Locally Advanced or Metastatic Solid Tumors

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STATISTICAL ANALYSIS PLAN
FOR PROTOCOL CD09_BASKET

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Protocol Number:	CD09_Basket	
Protocol Title:	Basket Study of Leronlimab (PRO 140) in Patients with CCR5+ Locally Advanced or Metastatic Solid Tumors	
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Plan Version:	SAP – Version 0.1		
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SAP Version:	SAP – Version 0.1
SAP Date:	20-Apr-2021

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

Statistician, [redacted]	Date
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ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation/Acronym	**Definition**

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol CD09_Baseket, conducted by CytoDyn Inc. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objectives of this plan are to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of 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 Council on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this Statistical Analysis Plan 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 2.0 / 14-May_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 study with 30 patients of leronlimab (PRO 140) in patients with CCR5+ locally advanced or metastatic solid tumors.

Leronlimab (PRO 140) will be administered subcutaneously as weekly dose of 525 mg until disease progression or intolerable toxicity. Subjects participating in this study will be allowed to receive/continue standard-of-care chemotherapy or radiotherapy 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 2-1.

(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 or cytologically confirmed locally advanced or metastatic solid tumors 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 CTC and CAML analysis.

Leronlimab (PRO 140) will be administered subcutaneously weekly by a licensed medical professional at clinic site or self-administered by subjects at home.

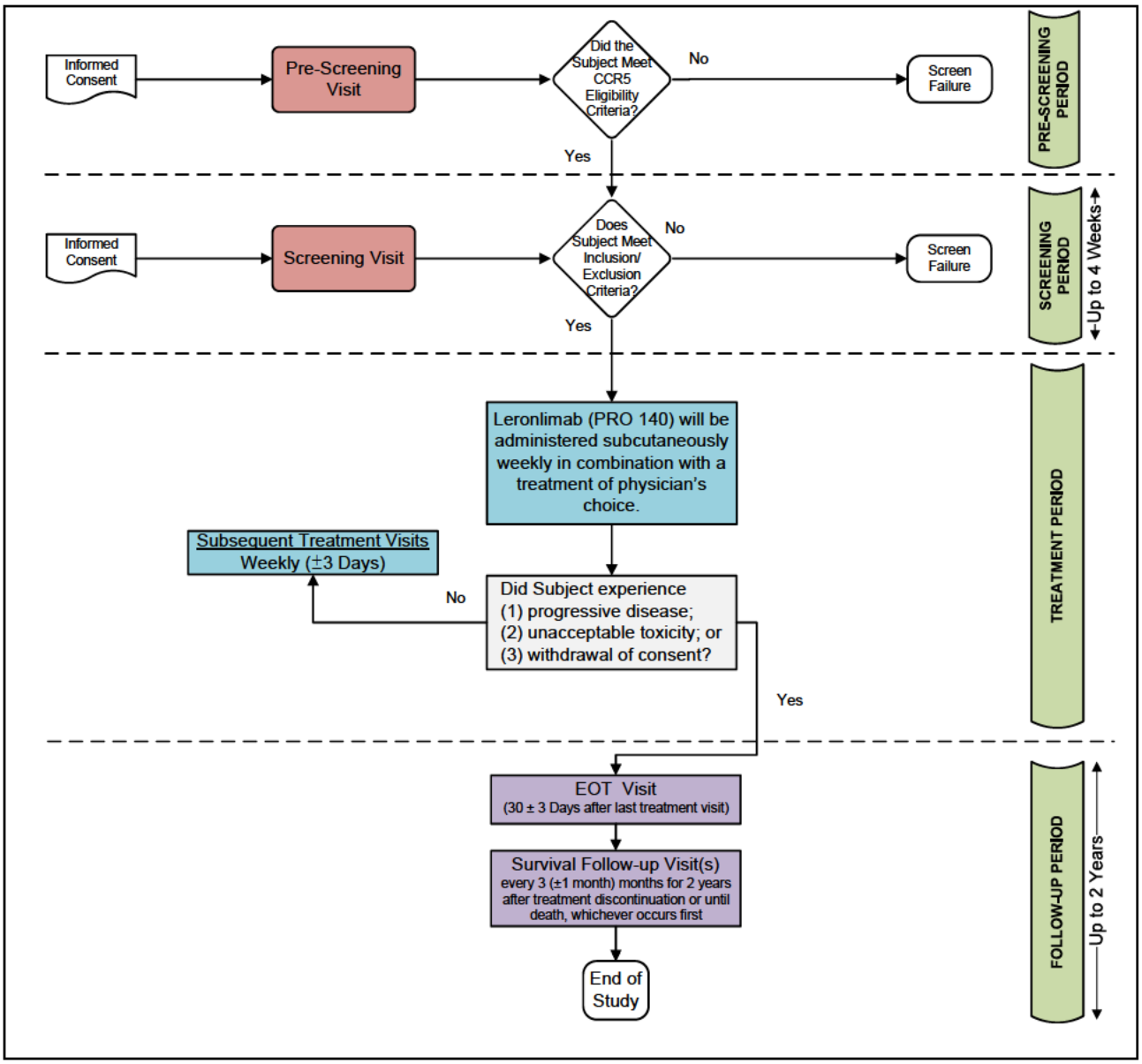
Note: All initial leronlimab (PRO 140) SC weekly injections must be administered at clinic. The remaining study treatment injections may be self-administered by subjects at home after proper training by a healthcare professional.

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.

A subject is considered to have completed the study once all survival follow-up visit assessments up to 2 years after treatment discontinuation have been performed or until death, whichever occurs first.

Figure 2-1: Study Flow Diagram



2.2 Treatment Groups

Eligible subjects will receive leronlimab (PRO 140) administered weekly at a dose of 525 mg SC, starting on Week 1 and every week thereafter, until disease progression or intolerable toxicity.

2.3 Randomization and Stratification

Not Applicable.

2.4 Blinding

Not Applicable.

2.5 Time to Unblinding

Not Applicable.

2.6 Protocol Objective(s)

2.6.1 Primary Objective

The primary objective of this study is to assess anti-tumor activity of Leronlimab (PRO 140) in the treatment of patients with CCR5-positive, locally advanced or metastatic solid tumors as part of a defined treatment protocol.

2.6.2 Secondary Objectives

The secondary objectives of this study are:

- To collect further safety, tolerability and efficacy data.
- To evaluate correlative studies for better treatment selection in future validation studies.

2.7 Outcome Measures

2.7.1 Efficacy Outcome Measures

The efficacy outcome measures in this study are:

- 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.

- 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+ locally advanced or metastatic solid tumors treated with leronlimab (PRO 140)

  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.

2.7.2 Safety Outcome Measures

The safety outcome measures in this study are:

- 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+ locally advanced or metastatic solid tumors.
  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

2.7.3 Exploratory Outcome Measures

- Measure immune biomarkers in CTCs, metastatic tissue and immune cells such as CAML and correlate with therapeutic benefit (PFS); and
- Assess changes in CTCs and CAML after treatment and perform correlative analysis of CCR5 expression

3. Sample Size Determination, Statistical Power, And Significance Level

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.

5. PRIMARY HYPOTHESIS TO BE TESTED

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

6. ANALYSIS POPULATIONS

6.1 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.

6.2 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

6.3 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, all collected data will be listed and 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 Outliers

Data points that appear to be outliers (i.e., clinically identified to be too small or too large) will be investigated and will not be excluded from the listings. If the clinician confirms that a data point is truly an outlier and is not clinically possible, two analyses will be performed, one with the outlier data point and one without it. Any such analysis will be clearly indicated and footnoted.

7.4 Handling of Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized to minimize missing data. Missing data will not be imputed.

7.5 Sensitivity Analysis

7.6 Multicenter Clinical Trials

This is a multi-center clinical trial with up to 10 centers in the United States (US).

7.7 Multiple Comparisons and Multiplicity

There will be no adjustment for multiple testing or multiplicity for this phase II trial. For all effectiveness endpoints, inference will be based on type I error rate of 0.05.

7.8 Covariates and Prognostic Factors

In the efficacy analysis, the baseline values will be used as covariates in the analysis of all efficacy outcome measures.

7.9 Subgroups

There is no prespecified subgroup analysis for this study. Subgroup analysis may be conducted as needed.

7.10 Standard Calculations

7.10.1 Age

Age will be calculated according to the formula noted below.

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

7.10.2 Body Mass Index (BMI)

BMI will be calculated using height (in cm) and weight (in kg) according to the formula noted below.

BMI (kg/m2) = Weight (kg)/[Height (cm)/100]^2

7.10.3 Change from baseline

Change from baseline will be calculated for each post baseline visit as follows:

Change From Baseline = Post baseline result at time - Baseline result

7.10.4 Percent Change from Baseline

Percent change from baseline will be calculated according to the formula noted below.

Percent change from Baseline = (Post baseline result at time - Baseline result) / Baseline result * 100

7.10.5 Time to Progression Free Survival (PFS)

Time to Progression Free Survival (PFS) in months will be calculated according to the formula noted below:

Time to Progression Free Survival = (Date of objective disease progression or death due to any cause, whichever occurs earlier – Date of first treatment + 1)/30.4

7.10.6 Time to new metastases (TTNM)

Time to new metastases (TTNM) will be calculated according to the formula noted below:

Time to new metastases (TTNM) = (Date of new metastases – Date of first treatment) + 1

7.10.7 Time to Overall Survival (OS)

Time to Overall Survival (OS) in months will be calculated according to the formula noted below:

Time to Overall Survival = (Date of death due to any cause – Date of first treatment + 1)/30.4

7.10.8 Overall Response Rate (ORR)

Overall Response Rate will be calculated according to the formula noted below:

Overall Response Rate (ORR) = Complete Response (CR) + Partial Response (PR)

7.10.9 Clinical Benefit Rate (CBR)

Clinical Benefit Rate (CBR) will be calculated according to the formula noted below:

Clinical Benefit Rate (CBR) = Complete Response (CR) + Partial Response (PR) + Stable Disease (SD)

8. STATISTICAL METHODS

All statistical analyses will be performed using SAS® for Windows, version 9.4 or later. All data collected during this study will be presented in subject data listings.

All the efficacy analyses presented here will be conducted using ITT and PP populations. All safety analyses will be conducted using the Safety population.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group. For categorical variables both frequencies and percentages will be presented by treatment group.

8.1 Summarizing Disposition and Baseline 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 trial. The following will be summarized by treatment group:

- The number of subjects who signed informed consent
- The number of subjects who are screen failures
- The number of subjects who received at least one study treatment
- The number of subjects who completed the study
- The number of subjects who discontinued prior to completion
    - Reasons for discontinuation prior to completion will also be summarized descriptively by treatment group.

The number of subjects in each analysis population will be summarized, reason for exclusion from analysis populations will be listed.

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

8.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major before un-blinding.

Protocol deviations for all randomized subjects will be listed as by-subject listing and major deviations 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

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, race, gender, disease characteristics etc.) will be presented as by-subject listing and summarized in Safety population. See Section 7.1 for baseline definition.

Tumor Imaging Assessment, Serum Pregnancy Test, and Tissue for CCR5 will be provided as by-subject listings.

8.1.4 Medical History

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by by system organ class (SOC) and preferred term (PT). Each subject will be counted only once within each PT or SOC.

8.1.5 Prior and Concomitant Medications

Prior medication is defined as any medications with an end date prior to the first treatment date.

All prior and concomitant medications recorded in the case report form will be listed and coded to the drug substance level (i.e., generic term) using the most recent version of WHO Drug dictionary, and summarized by treatment group and by the number and percentage of subjects taking each medication for the Safety population.

8.1.6 Extent of Exposure

All treatment administration data will be listed and summarized for the Safety population.

The duration (in days) of treatment administration will be determined per the following formula:

Duration = (date of last treatment administration – date of first treatment administration + 1

8.1.7 Study Treatment Compliance

Study treatment compliance will be determined per the following formula:

Compliance = [sum of all study drugs administered/ sum of all study drugs prescribed during the Duration of Exposure] x 100%

All accountability and compliance data will be listed and summarized for the Safety population.

8.2 Analysis of Efficacy Data

The efficacy analysis will be conducted on the Evaluable Population. The PP population will be used as a supportive analysis if there is at least 5% difference between the numbers of subjects in the two populations. Any observations excluded from the efficacy analyses will be listed as by-subject listings.

8.2.1 Primary Endpoint / Outcome Measure

All data from this endpoint will be presented as by-subject listing.

8.2.1.1 Progression free survival (PFS)

The time to progression free survival in months will be calculated using the formula in Section 7.10.5 and summarized descriptively.

The likelihood score test in the Cox proportional hazards model (which is the equivalent of the Log Rank test) will be used to compare the time to progression free survival between the treatment groups. Kaplan-Meier analysis will be used to depict the median time (days) to progression free survival.

The Progression free survival (PFS) will be presented and summarized descriptively.

8.2.1.2 Overall response rate (ORR) and clinical benefit rate (CBR)

The Overall response rate (ORR) and clinical benefit rate (CBR) will be calculated using the formula in Section 7.10.7 and 7.10.8, and summarized descriptively.

8.2.1.3 Time to new metastases (TTNM)

The Time to new meatastases will be calculated using the formula in Section 7.10.6 and summarized descriptively.

The likelihood score test in the Cox proportional hazards model (which is the equivalent of the Log Rank test) will be used to compare the time to new meatastases between the treatment groups. Kaplan-Meier analysis will be used to depict the median time (days) to new meatastases.

The proportion of new meatastases will be presented and summarized descriptively.

8.2.1.4 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 summarized descriptively and will be compared using ANCOVA.

8.2.1.5 Overall Survival

The Overall Survival will be presented and summarized descriptively.

The time to overall survival in months will be calculated using the formula in Section 7.10.7 and summarized descriptively.

The likelihood score test in the Cox proportional hazards model (which is the equivalent of the Log Rank test) will be used to compare the time to overall survival between the treatment groups. Kaplan-Meier analysis will be used to depict the median time (days) to overall survival.

8.3 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.

8.3.1 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 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) Sever adverse events
c) Related adverse events
d) Adverse events leading to treatment discontinuation
e) Adverse events leading to death

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.

8.3.2 Clinical Laboratory Evaluations

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

8.3.2.1 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.

8.3.2.2 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 safety laboratory data (by laboratory parameter):

- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTCAE grades
- Shift tables using Low/High/Nomal 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 CTCAE grades

8.3.2.3 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.

8.3.2.4 Individual Clinically Significant Abnormalities

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

8.3.3 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 (^{0}C), heart rate (bpm), respiratory rate (rpm).

8.3.3.1 Vital Signs Values over Time

Summary statistics of raw data and change from baseline values for each vital sign 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.

8.3.3.2 Individual Patient Changes on Notable Vital Sign Values

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 for by treatment group.

8.3.3.3 Individual Clinically Significant Abnormalities

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

8.3.4 Physical Examination

8.3.4.1 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.

8.3.4.2 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.

8.3.4.3 Clinically Significant Abnormalities

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

8.3.5 Electrocardiogram (ECGs)

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

8.3.5.1 ECG Values over Time

Summary statistics of raw data and change from baseline values for each ECG parameter will be presented by 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.

8.3.5.2 Individual Patient Changes on Notable ECG Values

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

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 using frequency and percentages 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) Increase >25% from baseline and HR >100 bpm at any post-baseline assessment
(2) Decrease >25% from baseline and HR <50 bpm at any post-baseline assessment

8.3.5.3 Individual Subject Changes on Interpretation

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.

8.3.5.4 Clinically Significant Abnormalities

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

8.3.6 Eastern Cooperative Oncology Group (ECOG) performance status

All data from Eastern Cooperative Oncology Group (ECOG) performance status will be presented as a by-subject listing. Change from baseline in Eastern Cooperative Oncology Group (ECOG) performance status from baseline to subsequent scheduled visits will be summarized descriptively.

8.3.7 Serum Pregnancy Test

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

8.3.8 Urine Pregnancy Test

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

8.3.9 Post Injection Site Evaluation by Investigator

All data from post injection site evaluation by investigator will be presented as a by-subject listing and/or summarized descriptively.

8.3.10 Injection Site Pain Assesssment

All data from injection site pain assessment will be presented as a by-subject listing and/or summarized descriptively.

8.3.11 Survival Status

All data from survival status will be presented as a by-subject listing and/or summarized descriptively.

8.4 Analysis of Exploratory Data

8.4.1 Measure immune biomarkers in CTCs, metastatic tissue and immune cells such as CAML and correlate with therapeutic benefit (PFS)

Measure immune biomarkers in CTCs, metastatic tissue and immune cells such as CAML will be summarized descriptively.

8.4.2 Assess changes in CTCs and CAML after treatment and perform correlative analysis of CCR5 expression

Changes in CTCs and CAML after treatment will be summarized descriptively and correlative analysis of CCR5 expression will be peformed.

9. APPENDIX 1

FIGURE 9-1: 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 [23]	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 X		30 Days (±3) after last treatment visit	Every 3 months [18]
Window			±3 days since last treatment																
Informed Consent [2]	X	X															Additional Treatment Visits (Section 4.3.2)		
Demographics and Baseline Disease Char.		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[19]	X[20]
Tumor Imaging Assessment [8]		X												X					X[20]
Complete Blood Count [9][24]		X	X[22]			X[22]			X[22]			X[22]			X[22]			X	
Biochemistry [10] [24]		X	X[22]			X[22]			X[22]			X[22]			X[22]			X	
Urinalysis [11] [24]		X	X[22]			X[22]			X[22]			X[22]			X[22]			X	
Serum Pregnancy test [12]		X																	
Urine Pregnancy test [12]			X			X			X			X			X				
Eligibility Assessment	X	X	X																
Enrollment / Cohort Assignment			X																
Blood sample collection for CTC and CAML Analysis [13]			X			X			X			X			X			X	
Tissue for CCR5 (archival or fresh biopsy)	X[14]																		

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 [23]	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 X		30 Days (±3) after last treatment visit	Every 3 months [18]
Window			±3 days since last treatment																
leronlimab (PRO 140) administration [15]			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Post Injection Site Evaluation by Investigator [16]			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Injection Site Pain Assessment [17]				X	X	X	X	X	X	X	X	X	X	X	X	X			
Survival status																		X	X[17]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X[21]
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 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 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 4-8 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 4-8 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 CTC and CAML analysis to be taken prior to treatment administration at T1 and every 3 weeks thereafter, and at the end of treatment (EOT).

[14] Archival 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.

[15] Leronlimab (PRO 140) is administered as subcutaneous injection in the abdomen weekly. A total of 525 mg (175 mg/mL) is delivered as two injections of 1.5 mL each on opposite sides of the abdomen.

[16] 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.

[17] Subject-perceived injection site pain (average pain since last treatment) will be assessed using the numeric pain rating scale 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.

[18] 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

[19] 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.

[20] 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.

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

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

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

[24] CBC, biochemistry, and urinalysis testing schedule (i.e., every 21 days) is allowed to be modified by the treating oncologist (or Investigator) based on standard of care chemotherapy regimen. Must be performed at least once every 28 days (4 weeks).

10. APPENDIX 2

10.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

SUBJECTS EXCLUDED FROM THE EFFICACY ANALYSIS (LISTINGS 16.2.3.X)

DEMOGRAPHIC DATA (LISTINGS 16.2.4.X)

INDIVIDUAL EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT LISTINGS (LISTINGS 16.2.7.X)

INDIVIDUAL LABORATORY MEASUREMENTS (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
- PHYSICAL EXAMINATION
- OTHER SAFETY

11. REFERENCES

1. ASA Ethical Guidelines for Statistical Practice (2016)
2. The Royal Statistical Society: Code of Conduct (2014)
3. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
4. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
5. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
6. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

12. VERSION HISTORY

This is the first draft version of this document.