CYTODYN

Protocol Cover Page

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)

Protocol Number: CD07_TNBC_CompassionateUse

Version: 4.0

Document Date: 14-May-2020

NCT Number: NCT04313075

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

Protocol Number:	**CD07_TNBC_CompassionateUse**
Version:	**4.0**
Date:	**14-May-2020**

Sponsor: **CytoDyn, Inc.**
1111 Main Street, Suite 660
Vancouver, Washington 98660
(360) 980-8524-Work
(360) 980-8549-Fax
www.cytodyn.com

Lead Principal Investigator: [redacted]

Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**CD07_TNBC_CompassionateUse**
Version:	**4.0**
Date:	**14-May-2020**

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

PROTOCOL APPROVAL FOR USE

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**CD07_TNBC_CompassionateUse**
Version:	**4.0**
Date:	**14-May-2020**

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Number _____

SPONSOR INFORMATION

CytoDyn, Inc.

1111 Main Street, Suite 660
Vancouver, Washington 98660
(360) 980-8524-Work
(360) 980-8549-Fax
www.cytodyn.com

CONTRACT RESEARCH ORGANIZATION INFORMATION

[redacted]

PROTOCOL SYNOPSIS

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)
Title of Study: 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)	
Planned Number of Subjects: 30 Subjects	**Study Development Phase:** Compassionate Use
Study Population: Patients with CCR5-positive, locally advanced or metastatic triple-negative breast cancer (mTNBC).	
Objectives: **Primary Objective:** 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 Objectives:** 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	
Trial Design: 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 525 mg until disease progression or intolerable toxicity. Treatment of Physician's Choice (TPC) is defined as the following drugs administrated according to local practice: eribulin, gemcitabine, capecitabine, paclitaxel, nab-paclitaxel, carboplatin, or atezolizumab (or other checkpoint inhibitors). 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.	

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)

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~~Figure 4-1~~.

- **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.

- **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.

- **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 – CAML 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.

- **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.

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)

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

Inclusion Criteria: Subjects are required to meet all of the following criteria for enrollment into the study:

1. Must have a histologically confirmed diagnosis of TNBC. Must demonstrate HER-2 negative (IHC 0, 1+, or fluorescence in situ hybridization (FISH) negative and ER< 1%, and PR < 1%, per ASCO/CAP criteria);

   Note: Patients with ER and/or PR <10% who have failed on endocrine therapy will also be eligible for participation in the study.
2. Demonstrate CCR5 + by IHC (>10% of primary or metastatic tumor cells shows membranous staining and/or high predominance of CCR5+ tumor-infiltrating leukocytes completed at the reference laboratory of [redacted]).

   Note: This test will be done as part of the pre-screening period. It will be performed in archival metastatic tissue. If archival tissue is not available then, fresh biopsy will be done;
3. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion (in case archival tissue is not available);
4. Patients with de novo (metastatic or stage IV at initial diagnosis) breast cancer OR Patients with locally recurrent or metastatic breast cancer who have been treated with up to 3 previous line of systemic therapies (including neo/adjuvant setting) and progressed or were intolerant to the latest treatment.

   Note: Patients with PDL-1+ that elect not to receive checkpoint inhibitor or are excluded for medical conditions will be eligible for participation in the study.
5. Patients must have measurable disease based on RECIST v1.1;
6. Female patients, ≥ 18 years of age;
7. Patients must exhibit a/an ECOG performance status of 0-1;
8. Life expectancy of at least 6 months;
9. Patients must have adequate organ and bone marrow function within 28 days prior to registration, as

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)

defined below:

- leukocytes ≥ 3,000/mcL;
- absolute neutrophil count ≥ 1,500/mcL;
- platelets ≥ 100,000/mcL;
- total bilirubin: within normal institutional limits;
- AST(SGOT) &ALT(SPGT) ≤ 2.5 X institutional upper limit of normal (ULN) (applicable to all patients, irrespective of liver disease or metastasis); and
- creatinine: within normal institutional limits.

10. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator.
11. Females of child-bearing potential (FOCBP) and males must agree to use two medically accepted methods of contraception with hormonal or barrier method of birth control, or abstinence, prior to study entry, for the duration of study participation and for 60 days after the last dose of study drug (Refer to Appendix 1). Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. NOTE: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
    - Has not undergone a hysterectomy or bilateral oophorectomy; and
    - Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months).
12. FOCBP must have a negative serum pregnancy test at Screening Visit and negative urine pregnancy test prior to receiving the first dose of study drug; and
13. Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

Exclusion Criteria: Subjects meeting any of the following criteria will be excluded from enrollment:

1. HER-2 overexpressed/amplified MBC (Section 17.2~~17.2~~ – Appendix 2 for guidelines from ASCO);
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 28 days prior to enrollment;
3. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)

composition to leronlimab (PRO 140) are not eligible;

4. Patients who have had prior exposure to CCR5 antagonists are not eligible;
5. Patients who have a known additional malignancy that is progressing or requires active treatment are not eligible. Patients who have had a prior diagnosis of cancer and if it has been <3 years since their last treatment are not eligible. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer;
6. Has an active infection requiring systemic therapy. Note: Patients must complete any treatment with antibiotics prior to registration;
7. Patients who have a known HIV positive status or known/ active Hepatitis B and/or C infection are not eligible;
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability;
9. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator;
10. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial; and
11. Is pregnant or breastfeeding, or expecting to conceive or have children within the projected duration of the trial, starting with the pre-screening or screening visit through the duration of study participation.

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)

Study Outcomes Measures:

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+ 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

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.

- 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

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)

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.

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.

Statistical Considerations:

Sample Size Determination and Rationale:

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.

Analysis Populations:

Name of Sponsor/Company: CytoDyn, Inc.	
Name of Study Product: Leronlimab (PRO 140) - Humanized monoclonal antibody to CCR5	
Protocol Number: CD07_TNBC_Compassionate Use	**Indication:** Metastatic Triple Negative Breast Cancer (mTNBC)

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

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 **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.

Statistical Methodology:

Adverse events will be coded using the most recent version of MedDRA. TEAEs will be summarized by study phase, cohort, System Organ Class, and preferred term. Safety is reviewed regularly by a DSMB. PFS will be calculated using Kaplan-Meier curves and the median PFS will be read from this curve. Response rates (overall response rate, clinical benefit rate) will be calculated using proportions and 95% confidence intervals. Time to new metastases and overall survival will also be analyzed using Kaplan-Meier curves. Exploratory serial blood markers will be related to PFS using Cox regression, and to response using logistic regression.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CAML	Cancer-Associated Macrophage-Like cell
C_{max}	Maximal Concentration
cART	Combination Antiretroviral Therapy
CBR	Clinical Benefit Rate
CCL5	C-C Chemokine Ligand Type-5
CCR5	C-C Chemokine Receptor Type-5
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DAPI	4,2-diamidino-2- phenylindole dihydrochloride
DFS	Disease Free Survival
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECL2	ExtraCellular Loop 2
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
ER	Estrogen Receptor
FDA	U.S. Food and Drug Administration
FI	Fluorescent Intensity

Abbreviation	Term
FISH	Fluorescence in Situ Hybridization
FOCBP	Females of Child-bearing Potential
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDR	Homology-Directed DNA Repair
HEENT	Head, Ears, Eyes, Nose, and Throat
HER2	Human Epidermal Growth Factor Receptor-2
HIPAA	Health Insurance Portability Accountability Act
HIV-1	Human Immunodeficiency Virus Type 1
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry assay
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection Site Reactions
ITT	Intent-to-Treat
IV	Intravenous
LAR	Legally Authorized Representative
LTF	Lost to Follow-up
mAb	Monoclonal Antibody
mCRC	Metastatic Colorectal Cancer
MSS	Microsatellite Stable
MTD	Maximum Tolerate Dose
Nt	N terminus
OBT	Optimized Background Therapy
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over the Counter
PFS	Progression Free Survival

Abbreviation	Term
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PR	Progesterone Receptor
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 AND BACKGROUND

1.1 STATEMENT OF INTENT

The design, conduct and reporting of this study shall be conducted in compliance with the protocol, International Conference on Harmonization/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing a Contract Research Organization (CRO).

1.2 BACKGROUND OF THE DISEASE

1.2.1. Triple Negative Breast Cancer (TNBC)

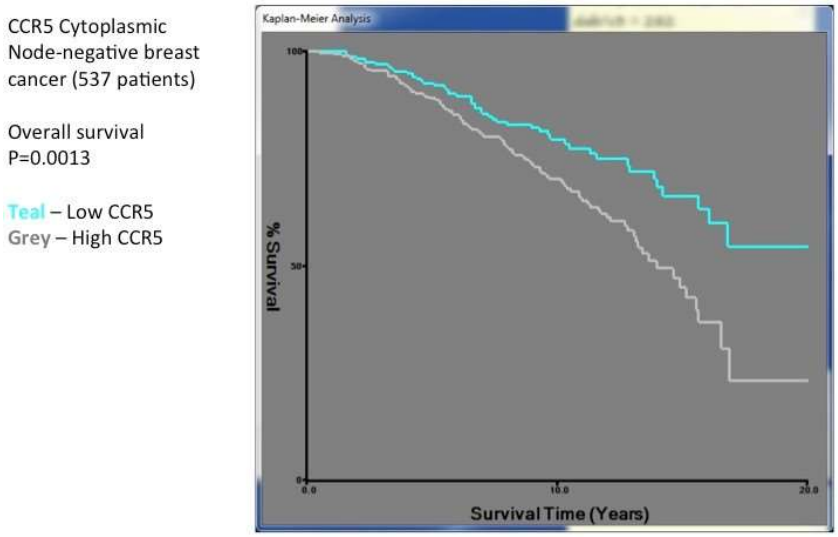
Clinical and molecular heterogeneity of breast cancer are translated in a diversity of clinical patterns of disease evolution and patient outcomes [Dawood, 2011] [Engstrom, 2013] [Harbeck, 2016]. TNBC is defined by the lack of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER-2) expression, which are known targets of endocrine therapies and anti-HER2 agents, respectively. Chemotherapy is still the main treatment option for TNBC patients. It accounts for 15-20% of breast cancer patients, a clinically highly relevant patient group that is characterized by younger age, unfavorable histopathological features including high histological grade, elevated mitotic count, high rate of p53 mutations and pushing margins of invasion with a shortened overall survival (OS) and disease free survival (DFS) compared to other breast cancer subgroups [Dawood, 2011] [Engstrom, 2013][Malorni, 2012]. For these reasons, TNBC account for a disproportionately high percentage of metastases, particularly distant recurrence, and death among patients with breast cancer. Moreover, in younger women TNBC has been described to occur more often with a high risk of recurrence and death, respectively, the latter with a peak incidence of 3 years after primary diagnosis. The pattern of recurrence involves more often visceral organs and less common bones compared to other breast cancer subtypes [Foulkes, 2010].

1.2.2. C-C Chemokine Receptor Type-5 (CCR5)

The process of cancer cell metastasis in different organs is a complex biologic event. Each tumor type presents a unique pattern of dissemination that has been well recognized for over a century as the “soil and seed” hypothesis [Paget, 1889]. However, only recently factors involved in this process have started to be understood. Preclinical and clinical data have suggested that chemokine receptors and its ligands, also referred as chemoattractant or chemotactic cytokines, are involved in the process of cancer cells tropism by specific organs [Moser, 2001][Neagu, 2015][Velasco-Velazquez, 2012][Chow, 2014]. Studies have correlated the altered expression of C-C Chemokine Ligand type-5 (CCL5) with disease progression in patients with breast cancer [Luboshits,

1999][Niwa, 2001][Zhang, 2009]. Immunofluorescence staining techniques are well established for CCR5 expression. Velasco-Velazquez et al have evaluated an analysis of a combined microarray database comprising 2,254 breast cancer samples and showed that expression of CCL5/CCR5 is higher in basal subtypes (over 58% of samples) of breast cancer compared to luminal subtypes [Velasco-Velazquez, 2012].

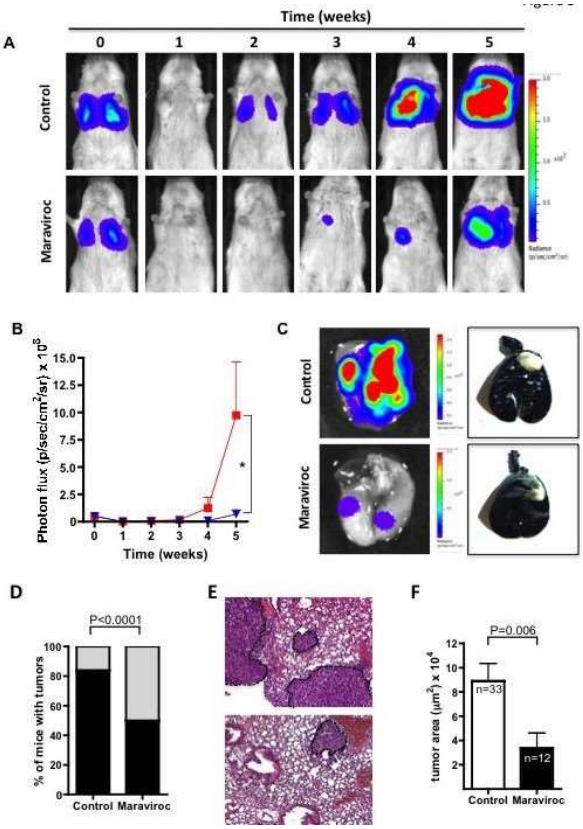
Figure 1-1: CCR5 over-expression correlates with poor survival). Immunohistochemical staining for CCR5 in 537 patients



CCR5 is also associated with programmed death-ligand 1 (PD-L1) [Halama, 2016]. Anti-PD-L1 antibodies have shown outstanding efficacy in the clinic for melanoma, non-small cell lung cancer and other cancers [Moser, 2001] [Garon, 2015] [Borghaei, 2015][Brahmer, 2015][Larkin, 2015]. Upregulation of PD-L1 may allow cancers to evade the host immune system and also inducing apoptosis in activated T cells. Preclinical data have shown that PD-L1 present in cancer is correlated with CCR5 abundance. Thus, blocking CCR5 may also contribute to increased immune response against tumor cells.

CCR5 has been shown to be sufficient to induce *in vitro* invasiveness and metastasis of breast cancer cells that is blocked by CCR5 inhibitors. Two distinct CCR5 inhibitors (Maraviroc, Vicriviroc) blocked CCR5 signaling and thereby blocked cells migration, invasion and metastasis in mice (Figure 1-2~~Figure 1-2~~) [Velasco-Velazquez]. The CCR5 inhibitors were shown to block homing of breast cancer cells to the lungs. The dose of CCR5 inhibitor used in these mouse models was the same as the dose used in patients for HIV treatment. Preclinical studies have also demonstrated that oncogenic transformation of immortal human breast cancer cells, with either Ha-Ras, c-Myc, ErbB2 (NeuT) or c-Src, induces the mRNA expression and protein abundance of CCR5 during the process of transformation [Velasco-Velazquez].

Figure 1-2: The CCR5 antagonist Maraviroc inhibits lung metastases in vivo



Another cancer hallmark that CCR5 presents potential role is the DNA repair pathways. This cancer characteristic attenuates apoptosis and contributes to chemotherapy resistance and tumor cells immortality. Preclinical data have separated CCR5+ vs CCR5- SUM159 cells by FACS and conducted mRNA gene expression profiling. GO term pathway analysis demonstrated CCR5+ cells induced the expression of pathways governing DNA repair. QT- PCR was used to quantitate a number of these genes and showed endogenous CCR5 enhances expression of the DNA repair genes, (FANCB, LIG3, POLE and CRY1) governing both homologous and non-homologous DNA repair, nucleotide excision repair and base excision repair. SUM159 cells stably transfected with CCR5 or control vector were compared for the DNA damage/repair response. Γ-radiation of SUM159 cells induced p-γH2AX, however CCR5-overexpressing cells showed reduced p-γH2AX at 24 hours. Treatment of SUM159 cells with the DNA intercalating anthracycline doxorubicin induced γH2AX phosphorylation, and CCR5-overexpressing cells showed less p-γH2AX than its control with 24 hours treatment. The DNA repair reporter, DR-GFP is used to measure homology-directed DNA repair (HDR). In order to measure HDR activity $CCR5^{+}$ SUM159 cells, the cells were co-transfected with the plasmid encoding I-SceI and the I-SceI based DNA repair reporter DR-GFP and stained with APC labeled anti-CCR5 antibody. GFP^{+} cells, generated by HDR of I-SceI induced double-strand DNA, were sorted by FACS into $CCR5^{-}$ and $CCR5^{+}$ populations. The percentage of $DR\text{-}GFP^{+}$ cells was increased in $CCR5^{+}$ or CCR5-

overexpressing cells compared with CCR5- or vector control cells [Robert, 2015]. The dramatic enhancement of DNA repair signaling by CCR5 activation may contribute to the resistance of a patient's tumor to chemotherapeutic agents.

1.2.3. Circulating Tumor Cells (CTCs) in Metastatic Breast Cancer (MBC)

The major treatment objectives in the advanced stage disease remain palliation of symptoms and improvement of quality of life. Importantly, breast cancer is a heterogeneous disease and long-term patient outcome can be influenced by various biological features, as well as by the extent and site of metastatic disease. Typically, widespread visceral disease is associated with symptomatic progression leading to deterioration of the performance status and short survival. Various molecular markers and blood-based tests have been investigated as surrogate for more aggressive disease, among them the most reliable appears enumeration of circulating tumor cells [Xuanmao, 2015].

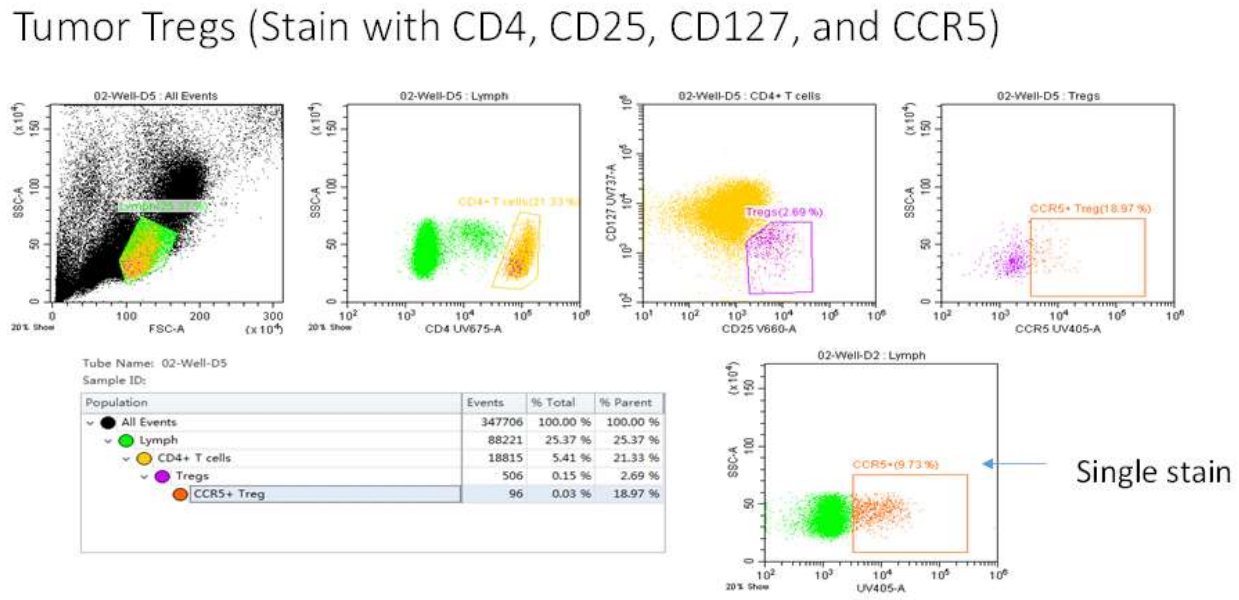
During the last decade, several techniques capable of detecting and quantifying circulating tumor cells (CTCs) in cancer patients have been developed. It has been proposed that subpopulation of CTCs with tumor initiating potential act as a central mediator of metastatic dissemination, giving rise to the formation of distant micrometastases, which subsequently generate overt detectable and frequently measurable lesions [Foulkes, 2010]. In support of this theory, multiple studies have shown that a number of CTCs higher or equal than 5 per 7.5 mL of blood, evaluated before starting systemic treatment, is associated with poor outcome in patients with metastatic breast cancer [Xuanmao, 2015]. In addition, high CTC counts are associated with greater metastatic tumor burden, expressed as number of metastatic sites [Moser,2001][Neagu, 2015]. Importantly, despite this association, the prognostic value of CTCs is independent from the initial number of metastatic sites [Moser,2001][Neagu, 2015]. Moreover, a recent pooled analysis of 1944 patients was performed confirming those data [Cristofanilli, 2004]. The authors created a clinicopathological prognostic model to determine the added impact of CTCs for PFS and OS. They found that adding CTC count (<5 or ≥ 5) to their predictive model significantly increased the prognostication for OS and PFS. The prognostic value of CTCs was consistent across all subtypes of disease. Finally, in the multivariate analysis, CTC count was the strongest prognosticator for PFS and OS. Furthermore, continued elevation of CTCs is known to be associated with a poor prognosis as well as a sign of chemoresistance [Bidard, 2014].

CTCs enumeration will be used as a measure of tumor cells escaping immune control and released into the blood. CTCs enumeration is used as a surrogate of metastasis and as a measure of the efficacy of therapy. CCR5 has also been implicated in the migration of tumor cell from blood into tissues so if CTCs are reduced by therapy but still present, a favorable result would be that they are no longer CCR5 positive due to receptor blockade by leronlimab.

1.2.4. CCR5+ Tumor-Infiltrating Leukocytes

The role of CCR5 blockade of the CCL5-CCR5 pathway in immune control of tumors have been defined in several publications in the peer-reviewed medical literature [Mañes, 2003]. CCR5 on tumor cells especially those that evade local immune control in the primary tumor leads to CCR5 positive circulating tumor cells that have the capability to disseminate and migrate into distant tumor sites again through the CCL5-CCR5 axis. Previous research and current data has also identified other immune mediated anti-tumor effects from CCR5 blockade [Lanitis, 2017, Halama, 2016]. Previous published reports suggest CCR5 expression on Treg cells which migrate into tumors due to the expression of CCL5 by lymphocytes [de Oliveira, 2017, Del Prete, 2017, Lanitis, 2017]. Tregs are responsible for minimizing or eliminating the anti-tumor effects of CD8 T-cells now restored by blockade of PD-L1/PD-1 by the new class of immune-oncology drugs [de Oliveira, 2017]. Further, blocking CCR5 on tissue associated macrophages (TAMS), one of the major cells in the tumor microenvironment that suppresses the T-cell mediated anti-tumor immune response, restores the anti-tumor activity by re-programming the TAMs [Lanitis, 2017, Walens, 2019]. Data from novel 24-color flow cytometry assay performed on single cell suspensions created with IVD IncellPREP device, confirmed the expression of CCR5 on Tregs from the tumor microenvironment in lung, breast, and bladder cancer samples. This technology or CCR5 immunohistochemistry of biopsies already obtained has allowed to selectively choose patients with CCR5 expression not only on tumor but on intra-tumor immune cells in the tumor microenvironment.

Figure 1-3: Tumor Tregs (Stain with CD4, CD325, CD127, and CCR5)

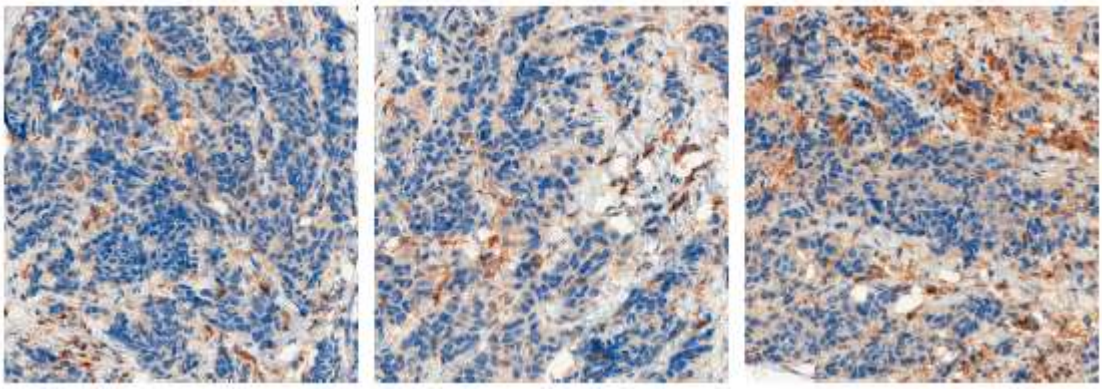


Because of the multitude of different mechanism CCR5 blockade may promote anti-tumor activity, immune control, and metastasis, the inclusion criteria has been expanded to encompass these varied mechanisms that may all lead to improved clinical response.

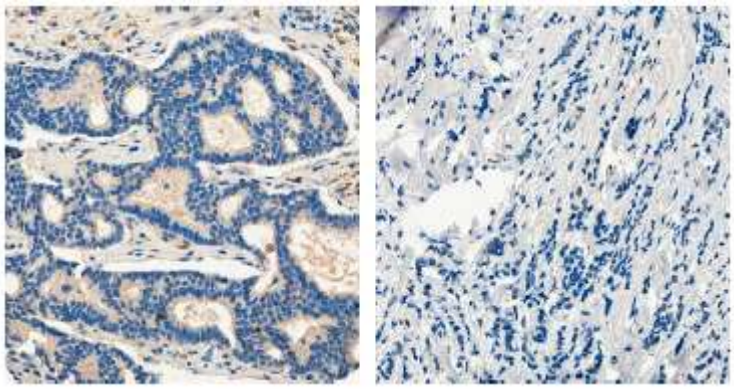
Below are the representative IHC staining images showing high predominance of CCR5 positive tumor infiltrating leukocytes in Triple Negative Breast Cancer tissue samples:

Figure 1-4: IHC staining showing high predominance of CCR5+ tumor infiltrating leukocytes in TNBC (Subject 1)

- Subject 1: Representative images of IHC for CCR5



- Negative Control CCR5



- Positive Control CCR5

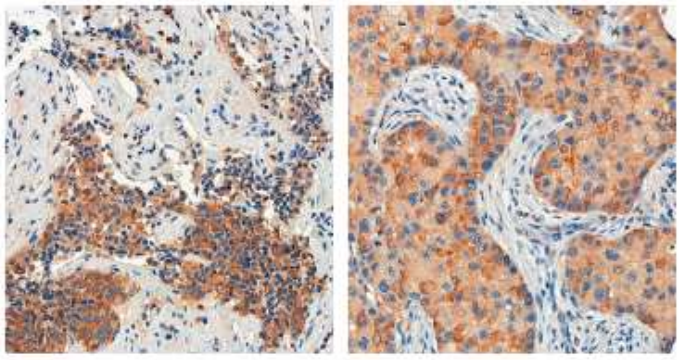
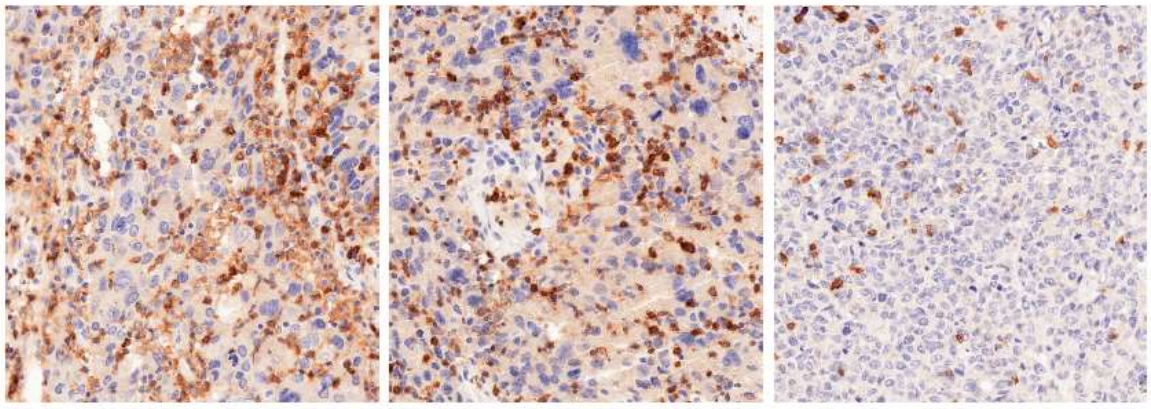
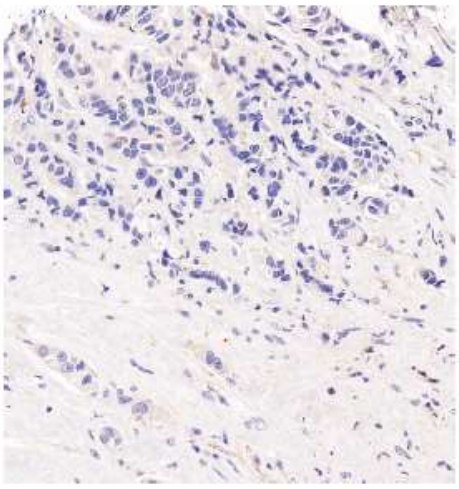


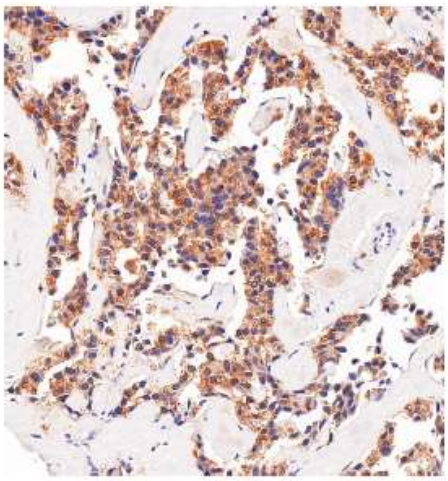
Figure 1-5: IHC staining showing high predominance of CCR5+ tumor infiltrating leukocytes in TNBC (Subject 2)

- Subject 2: Representative images of IHC for CCR5



- Negative Control CCR5
- Positive Control CCR5





1.3 STUDY TREATMENTS

1.3.1. Leronlimab (PRO 140)

Leronlimab (PRO) 140 is a humanized IgG4,κ monoclonal antibody (mAb) to the C-C chemokine receptor type 5 (CCR5), under development as a therapy for human immunodeficiency virus (HIV) infection.

Leronlimab (PRO 140) binds to the N terminus (Nt) and the extracellular loop 2 (ECL2) domain of the CCR5 cell surface receptor that HIV-1 uses to gain entry to a cell. Leronlimab (PRO 140) (binding to CCR5 blocks viral entry by interfering with the final phase of viral binding to the cell surface prior to fusion of the viral and cell membranes. Leronlimab (PRO 140) has been administered intravenously or subcutaneously to more than 750 healthy and HIV-1 infected individuals in Phase I/II/III studies. The drug has been well tolerated following intravenous administration of single doses of 0.5 to 10 mg/kg or up to 700 mg weekly doses as subcutaneous (SC) injection. Overall, 324 subjects have been exposed to leronlimab (PRO 140) 350 mg SC weekly dose with the longest duration of exposure lasting 4 years. Similarly, more than 250 and 150 subjects have been exposed to leronlimab (PRO 140) 525 mg and 700 mg SC weekly dose, respectively.

1.4 PRE-CLINICAL STUDIES OF LERONLIMAB (PRO 140)

In vitro and *in vivo* preclinical studies have been conducted to determine the pharmacokinetic, immunogenicity, and toxicity profiles of leronlimab (PRO 140) following IV and SC administration. Several acute and chronic toxicity studies have been conducted to support the clinical development plan.

Acute toxicity of leronlimab (PRO 140) was evaluated in New Zealand rabbits, following IV administration of 5 or 15 mg/kg. Chronic toxicity was evaluated in cynomolgus monkeys following biweekly administration of IV doses up to 10 mg/kg for six months and biweekly administration of various SC doses up to 50 mg/kg for 24 weeks. The drug was generally well tolerated. Biweekly administration of IV doses up to 10 mg/kg for six months resulted in minimum to mild lymphoid hyperplasia in assorted lymph nodes and spleen, which was considered an expected immune response to a foreign protein. Biweekly administration of SC doses up to 50 mg/kg for 24 weeks resulted in minimum injection-site reactions (minimal, multifocal, mononuclear cell infiltrates in the subcutis), which were considered due to an inflammatory response to the injected antigen. Monkeys tolerated treatment with leronlimab (PRO 140) for 24 weeks without evidence of local or systemic toxicity. Leronlimab (PRO 140) caused no mortality, cageside observations, in-life injection-site observations, or gross pathologic findings. Chronic treatment with leronlimab (PRO 140) did not affect body weight, food consumption, hematology, clinical chemistry or coagulation parameters.

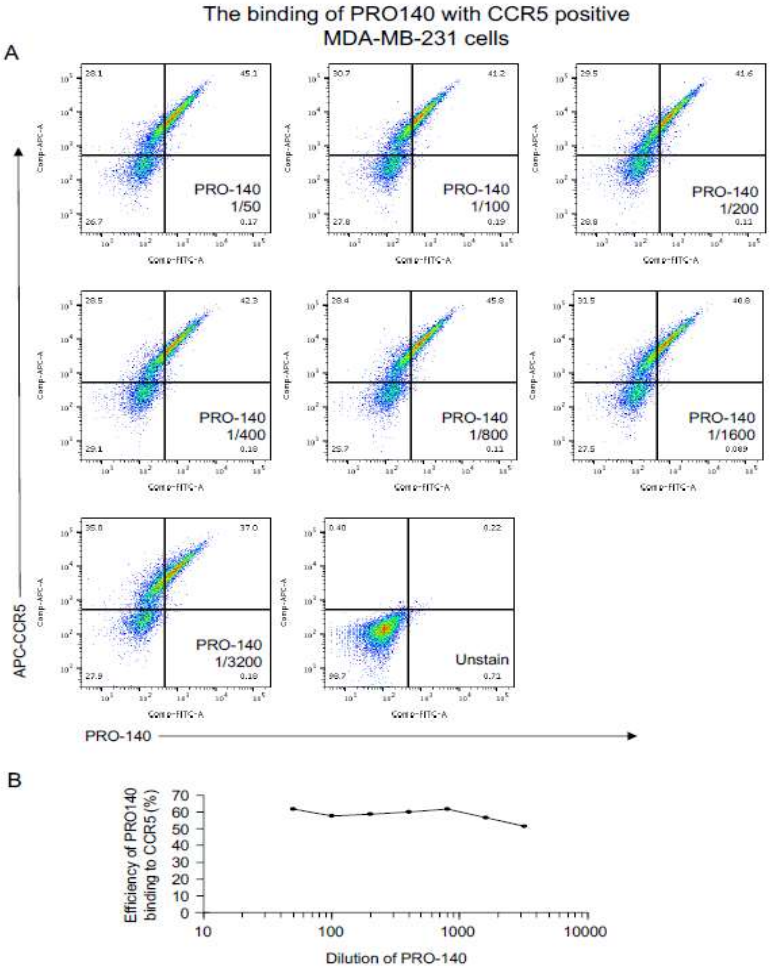
Both IV and SC administration resulted in elimination half-lives of approximately 200 hours, and overall exposure increased with increasing doses. Following SC administration of leronlimab (PRO 140) in monkeys, the maximal concentration (C_{max}) was achieved within 56 hours and bioavailability for leronlimab (PRO 140) after SC dosing was approximately 70%.

1.4.1. Effect of PRO140 on human CCR5 in breast cancer cells, MDA-MB-231

1.4.1.1 PRO140 binding to human CCR5 in human breast cancer cells

Figure 1-6: PRO-140 binds human CCR5 in human breast cancer cells.

Validation of PRO140 binding to CCR5 positive cells was assessed by FACS analysis. MDA-MB-231 stably expressing a human CCR5 expression vector was double stained with a commercial APC-conjugated mouse anti-human/mouse/rat CCR5 antibody and PRO140. Alexa Fluor 488 conjugated anti-human IgG was used as secondary antibody of PRO140. PRO 140 was diluted from 1/50 to 1/3200. (B) The efficiency of PRO140 binding to the CCR5 positive cells.



In order to determine the binding of PRO140 with human CCR5 in breast cancer cells, MDA-MB-231, a human triple-negative breast cancer cell line, was stably transfected with a human CCR5 expression vector as a model system. A commercial APC conjugated mouse anti-human/mouse/rat CCR5 antibody was used as a positive control to assess CCR5 positive cells. MDA-MB-231-CCR5 cells were stained with both APC-αCCR5 and PRO140 using a dilution from 1/50 to 1/3200 (Figure 1). Alexa Fluor 488 conjugated mouse anti-human IgG was used as secondary antibody to measure PRO140 binding cells. Analysis of PRO140 binding with CCR5 by FACS is shown in Figure 1. The efficiency of PRO140 binding with CCR5 was calculated as the ratio of Alexa Fluro 488 positive cells to APC positive cells. The efficiency of PRO140 binding to CCR5 positive cells was 62% at 1/800 dilution (Figure 1-6~~Figure 1-6~~A, B). These results demonstrate that PRO140 binds with human CCR5.

1.4.1.2 PRO140 blocks human CCR5 mediated signaling in human breast cancer cells.

CCR5 activation induces calcium flux [Mueller, 2002][Petkovic, 2004]. To assess the effects of PRO140 on CCR5 function, we measured the calcium responses induced by CCL5 in MDA-MB-231-CCR5 cells with or without PRO140 by living cell image (Figure 1-7~~Figure 1-7~~). Fluo-4 was

used as calcium concentration indicator. The CCR5 antagonist, Vicriviroc, was used as a positive control (Figure 1-7~~Figure 1-7~~).

MDA-MB-231-CCR5 cells were labeled with calcium indicator Fluo-4 and monitored under fluorescent inverted microscope with the incubator chamber at 37ºC and 5% CO2. For treated samples, a CCR5 inhibitor, either PRO140 or Vicriviroc, was added 30 minutes prior to the experiments. Video of living cells was taken at 20 sec intervals. CCL5 was added after 6 frames of the video, and FBS induced calcium responses were used as positive control. A representative example is shown in Figure 1-7~~Figure 1-7~~. Relative intracellular Ca2+ concentration was determined by the changes in fluorescent intensity (FI) of Fluo-4-AM and was calculated as (Fit – FI0)/FI0. Quantitative analysis of calcium responses induced by CCL5 are represented in Figure 1-7~~Figure 1-7~~ (B) control, (C) PRO140, and (D) Vicriviroc. Data is shown as mean ±SEM from 10-12 cells.

The results showed that PRO140 can block CCL5 induced calcium responses in MDA-MB-231-CCR5 cells at 1/100 dilution. (1.23±0.10, N=10 for control cells and 0.54±0.13 N=12 for PRO140 treated cells. P<0.001 at calcium peak induced by CCL5).

1.4.1.3 PRO140 blocks human CCR5 mediated invasion of extracellular matrix in human breast cancer cells.

Our previous studies using CCR5 specific small molecule inhibitors demonstrated that CCR5 is required for the invasion of extra-cellular matrix in both breast and prostate tumor models [Sicolo, 2014][Velasco-Velazquez, 2012]. Cancer cell invasion into the extra-cellular matrix is a key step of tumor metastasis [Zetter, 1990]).

MDA-MB-231 cells were used to test the ability of PRO140 to block cell invasion in a 3D-matrigel assay. CCL5 was used as chemoattractant to induce the invasion. Vicriviroc, a small molecule inhibitor of CCR5, was used as a form of positive control.

The results showed that PRO140 can block CCL5 induced MDA-MB-231 breast cancer cell invasion with similar efficacy as Vicriviroc (Figure 1-8~~Figure 1-8~~A, B) (855±9, N=8 for control vs 855±9, N=9 for PRO140, P <0.001). We also tested the effects of different doses of PRO140 on breast cancer cell invasion, and the results showed that both a 1/500 and a 1/1000 dilution of PRO140 can effectively block MDA-MB-231 cell invasion (Figure 1-8~~Figure 1-8~~C, D). Data is shown as mean ± SEM of the distance of cell invasion.

Figure 1-7: PRO140 blocks human CCR5 mediated signaling in human breast cancer cells.

The effects of PRO140 on CCL5 induced Ca^{+2} responses. MDA-MB-231 stable expressing CCR5 cells was labeled with Calcium indicator Fluo-4 and monitored under fluorescent inverted microscope with incubator chamber at 37oC and 5% CO2. Video of living cells was taken with 20 sec intervals. 30 minutes prior to the experiments, PRO140 or Vicriviroc was added. CCL5 was added after 6 frames of the video and FBS induced calcium responses were used as

a positive control. A representative example is shown. (B-D) quantitative analysis of calcium responses induced by CCL5 in control (B), PRO140 (C) or Vicriviroc (D) treated cells. Data is shown as mean ±SEM from 10-12 cells.

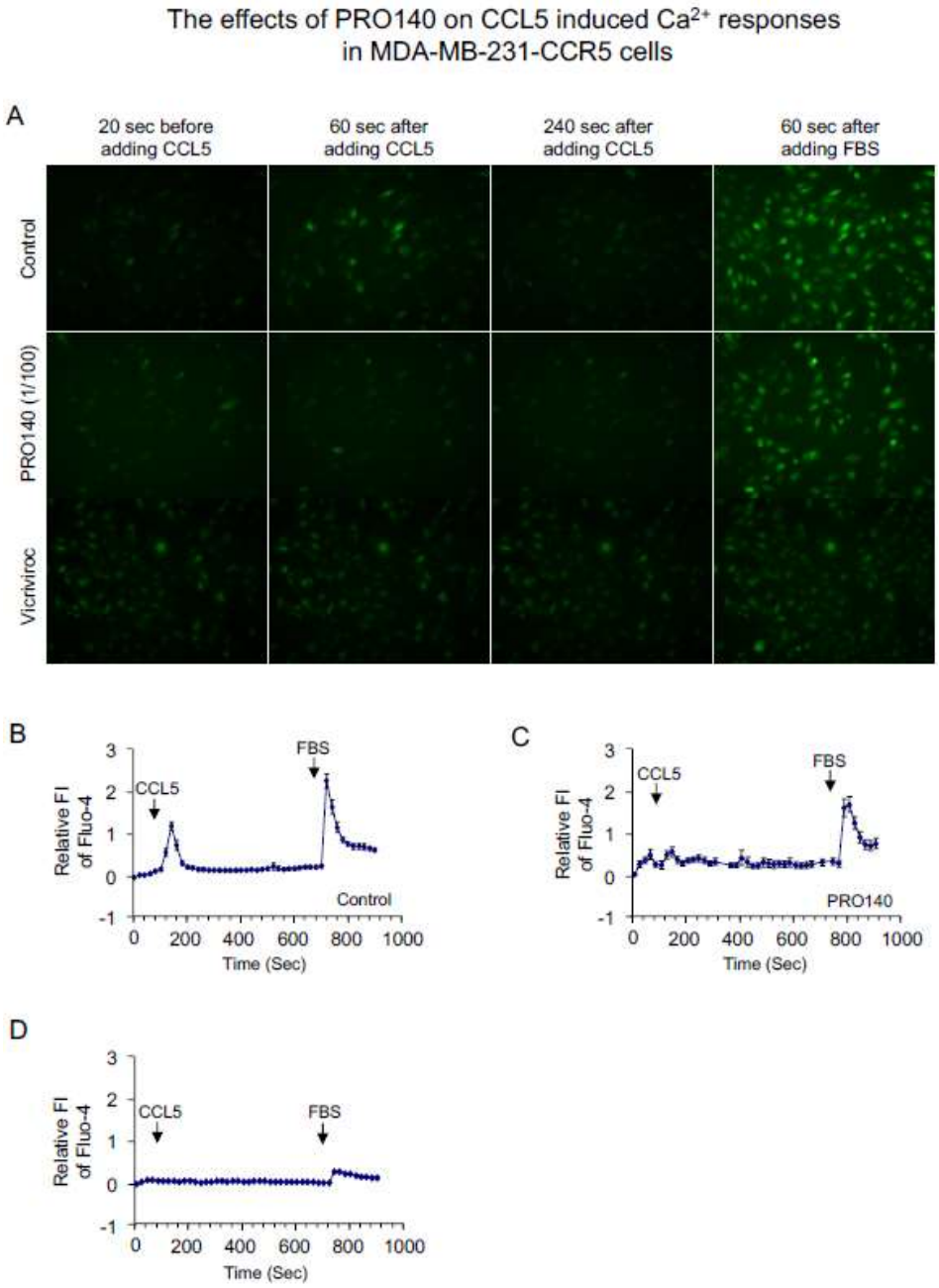
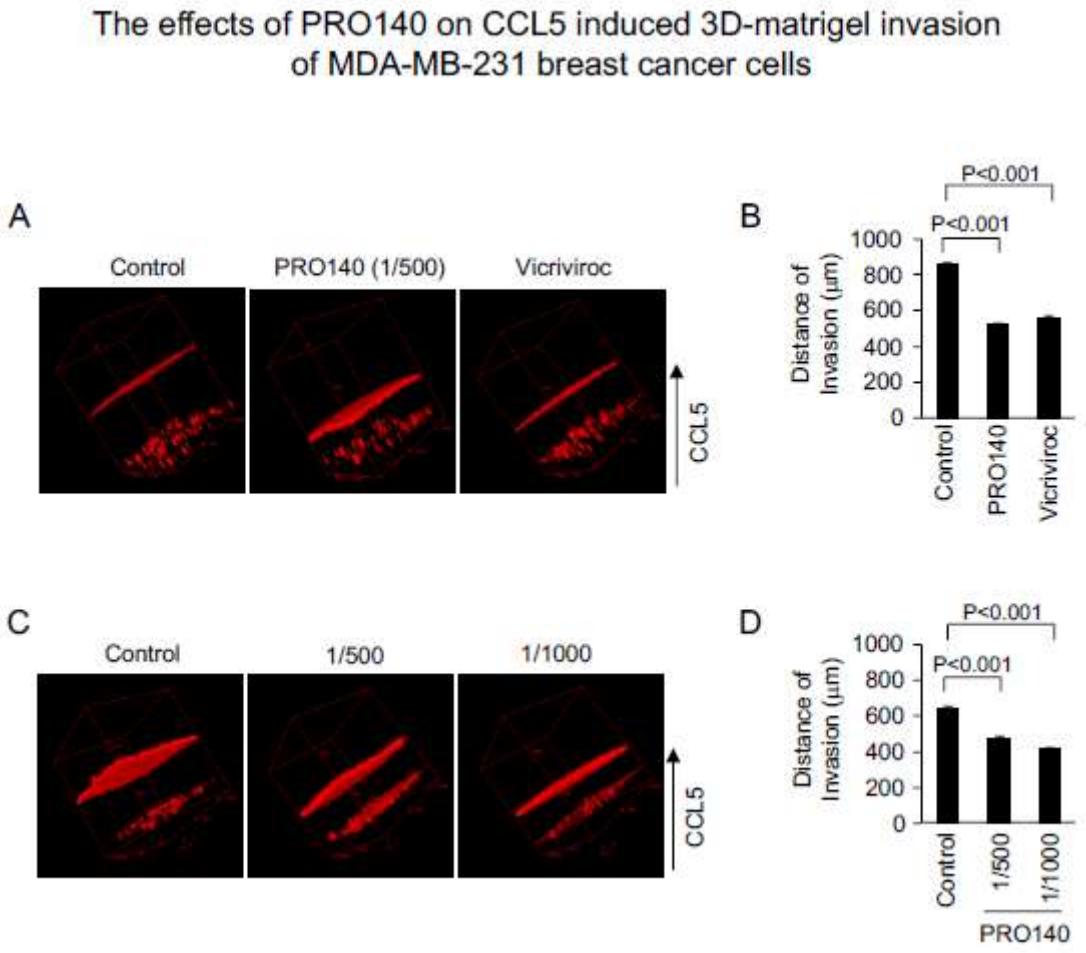


Figure 1-8: PRO140 blocks CCL5-induced breast cancer cell invasion

3D reconstruction of CCL5-induced invasion into collagen I gels by MDA-MB-231 breast cancer cells in presence of PRO140. CCL5 was used as chemoattractant. (A, B) The comparison of the effects of PRO14 and Vicriviroc. (C, D) The effects of different doses of PRO140 is shown. Data is shown as mean ± SEM of the distance of cell invasion.



1.4.2. Effect of PRO 140 on Growth of SW480 Human Colon Carcinoma Xenografts

A study was conducted to determine the anti-tumor activity of PRO 140 humanized monoclonal antibody against CCR5 in mouse xenograft models of SW480 human colon carcinoma grown in immunocompromised mice. The study was conducted in four parts, using different mouse strains, drug doses, and drug schedules.

SW480 human colon carcinoma cells (ATCC) were expanded in culture (DMEM, 10%FBS, antibiotic, antimycotic) and were inoculated subcutaneously (2 million per site, s.c.) in the flanks of male NCr nu/nu mice (Taconic), and male NOD-scid-IL2Rg (NSG) mice (Jackson). Mice were randomized to receive Control human IgG or PRO 140 intraperitoneal injection (i.p.) twice per week (Mon, Thu). Tumor diameters were measured 3 times weekly (Mon, Wed, Fri) with calipers, and tumor volume calculated using the formula for a prolate spheroid. The body weight of mice was determined weekly (Wed).

In Part 1 (high dose, early Rx) of the study, 2 mg PRO 140 i.p. was administered twice weekly, starting at Day 1 in 16 athymic nude mice. Part 2 (high dose, late Rx) included 8 athymic nude mice receiving 2 mg PRO140 i.p administered twice weekly, beginning Day 21.

In Part 3 (low dose, early Rx), 0.2 mg PRO 140 i.p was administered, beginning on Day 1, twice weekly in 16 athymic nude mice. Lastly, in Part 4 (high dose, early Rx), 16 NSG mice received 2 mg PRO 140 i.p, twice weekly, beginning Day 1.

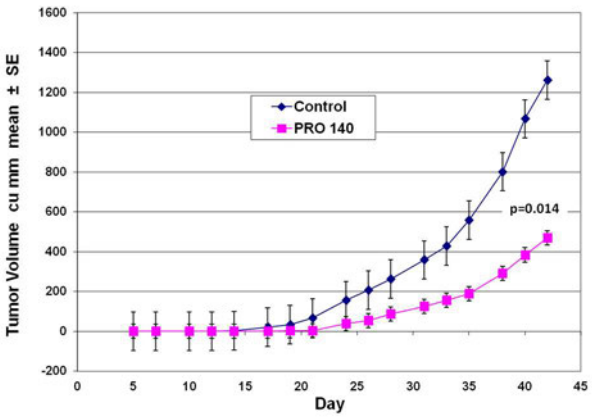
PRO 140 dosage was calculated using "Representative Surface Area to Weight Ratios (km) for Various Species" from: Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man, Cancer Chemother Rep. 1966;50:219-44; and the National Cancer Institute Developmental Therapeutics Program http://dtp.nci.nih.gov

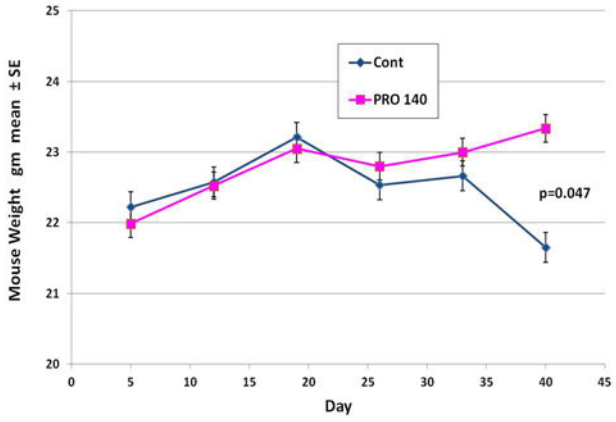
Starting with the human dose of PRO 140 = 5.8 mg/kg x 12 (man-to-mouse conversion factor) = 69.6 mg/kg mouse dose. Average mouse = 0.025 kg, therefore 69.6 mg/kg x 0.025 kg = 1.74 mg (mouse single dose). This was rounded up to 2.0 mg and designated as the high dose. A low dose (0.2 mg) was also tested. As control antibody, IgG derived from human serum was used (>95% SDS-PAGE, Sigma, I4506).

In Part 1, administration of PRO 140 (2 mg i.p. twice a week) induced a 62.8% reduction in SW480 tumor volume by day 42 (p=0.014). Mice receiving PRO 140 exhibited normal weight gain over the course of the study, whereas mice receiving non-specific IgG lost weight during the second half of the study (p=0.047).

Figure 1-9: Part 1: SW480 Human Colon Carcinoma Xenografts Grown in NCr Nude Mice

PRO 140 2 mg i.p. Twice/Wk, Started Day 1, n=16 Tumors/Group

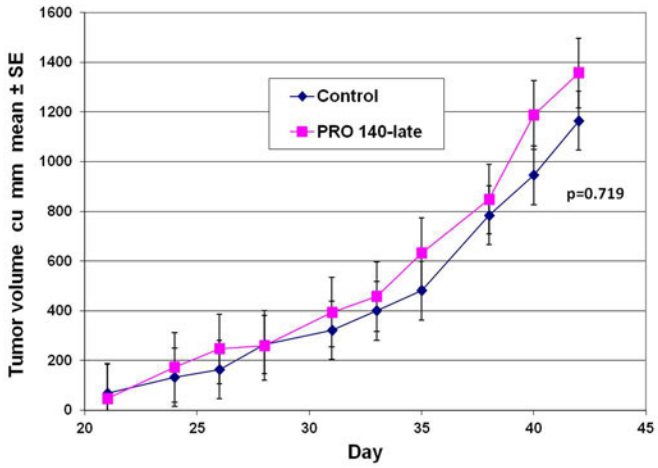




During Part 2, treatment of larger established tumors (volume: Cont 68.5 ± 47.25, PRO 140 47.25 ± 34.89 mm^3) with PRO 140 (2 mg i.p. twice a week) commencing on day 21, did not result in significant inhibition of tumor growth (p=0.719).

Figure 1-10: Part 2: SW480 Human Colon Carcinoma Xenografts Grown in NCr Nude Mice

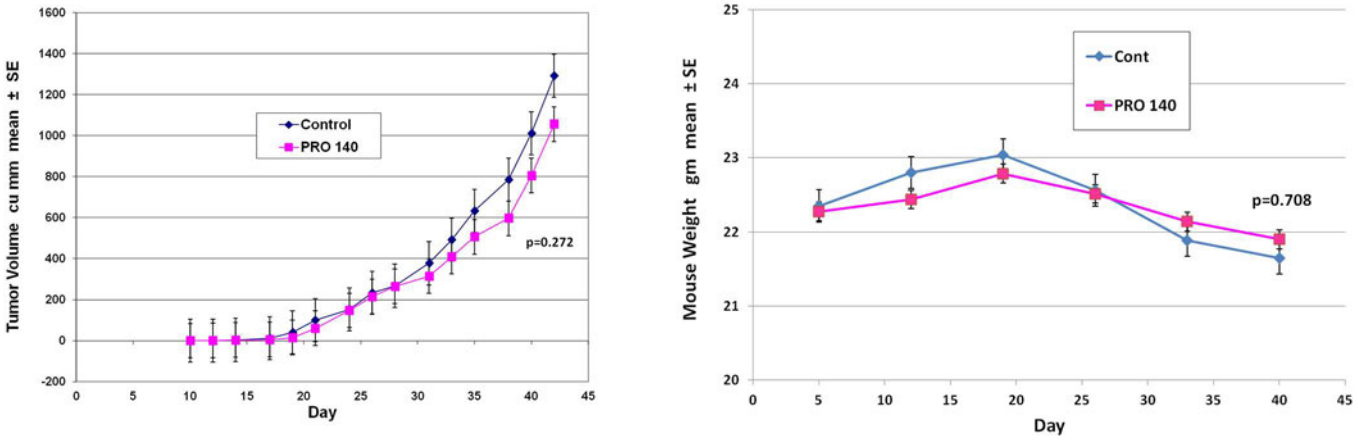
PRO 140 (2 mg i.p. Twice/Wk), Started Late (D21), n= 8 Tumors/Group



In Part 3 of the study, administration of PRO 140 at a reduced dose (0.2 mg i.p. twice a week) induced an 18.3% reduction in SW480 tumor volume by day 42, but did not reach statistical significance (p=0.272). During tumor progression in the second half of the study, both groups exhibited similar degree of weight loss (p=0.708).

Figure 1-11: Part 3: SW480 Human Colon Carcinoma Xenografts Grown in NCr Nude Mice

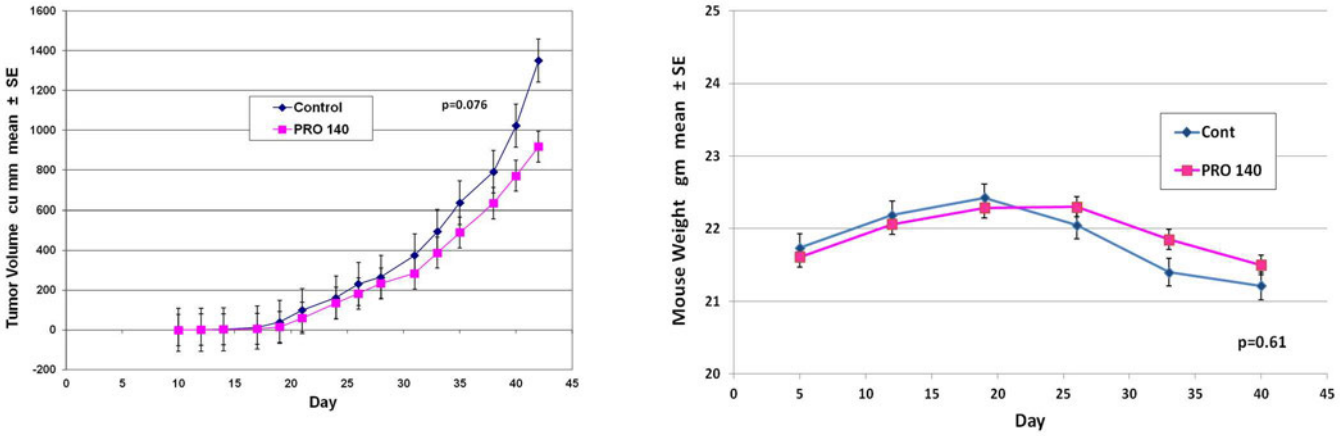
PRO 140 0.2 mg i.p. Twice/Wk, Started Day 1, n=16 Tumors/Group



For Part 4, switching from nude mice (lack T cells) to a more immunosuppressed host (NSG lack T, B, NK cells) resulted in loss of PRO 140 anti-tumor efficacy. There was a 32% reduction in tumor volume in the PRO 140 groups compared to control, but this did not reach statistical significance (p=0.076). There was a similar degree of weight loss in both treatment groups (p=0.61).

Figure 1-12: Part 4: SW480 Human Colon Carcinoma Xenografts Grown in NSG Mice

PRO 140, 2 mg i.p. Twice/Wk Started Day 1, n=16Tumors/Group



1.4.3. Clinical Studies with leronlimab (PRO 140)

Current human experience with leronlimab (PRO 140) consists of nine completed and six ongoing clinical trials, mostly on healthy subjects or HIV-1 positive subjects. These studies are summarized in Table 1-1~~Table 1-1~~ and Table 1-2~~Table 1-2~~ (pages 46-47). In all clinical trials, the majority of adverse events (Aes) have been mild or moderate. No dose-limiting toxicities or patterns of drug-related toxicities were observed. Antiviral activity was potent, rapid, prolonged, dose-dependent, and highly significant.

1.4.4. PRO 140 1101 Study

For the first-in-human trial, PRO 140 1101, the drug was administered IV at 0.1, 0.5, 2.0, or 5.0 mg/kg to healthy subjects and was generally well tolerated, non-immunogenic, and without clinically relevant toxicity. Treatment Emergent Adverse Events (TEAEs) did not increase with rising PRO 140 dose levels. Seventy-five percent (75%) of subjects reported TEAEs, most of which were deemed unrelated to study treatment by the investigator.

1.4.5. PRO 140 1102 Study

For PRO 140 1102, the majority of Aes, other than injection-site reactions, were considered mild and possibly related to drug administration. The majority of injection-site reactions were considered mild, self-resolving, and definitely related to drug administration. PRO 140 derived

from Chinese Hamster Ovary (CHO) cells and administered at 100 mg/mL was generally well tolerated in healthy, normal volunteers. Overall, PRO 140 administered SC using Autoject® 2 appeared better tolerated than manual injection.

1.4.6. PRO 140 1103 Study

In PRO 140-1103, administration of PRO 140 at 350 mg using Autoject® 2 appeared well tolerated. Manual injections, on the other hand, were associated with a greater number of Aes. There did not appear, however, to be any substantial difference in subject perception of pain or discomfort related to site of drug administration. No anti-PRO 140 antibodies were detected in any subjects in this study. There was a tendency of higher exposure associated with SC administration of PRO 140 at 350 mg in the abdomen and the thigh. A higher number of Aes were associated with injections in the arm. Based on these observations, thigh and abdominal administration of PRO 140 were preferred over arm injection.

1.4.7. PRO 140 1302 Study

The initial proof-of-concept study was a randomized, double-blind, placebo-controlled study in subjects with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks [Jacobson, 2008]. Subjects (n=39) were randomized to receive a single IV injection of placebo or PRO 140 at doses of 0.5, 2, or 5 mg/kg. Subjects were monitored for antiviral effects, safety, and PRO 140 pharmacokinetics (PK) for 58 days.

PRO 140 demonstrated potent, rapid, prolonged, and dose-dependent antiviral activity. Intravenous PRO 140 was generally well tolerated. No drug-related serious events or dose-limiting toxicity was observed [Jacobson, 2008]. The most common adverse events (headache, lymphadenopathy, diarrhea, and fatigue) were observed at similar frequencies across the placebo and PRO 140 dose groups. There was no significant effect on QTc intervals or other electrocardiographic parameters, and there were no remarkably laboratory findings.

1.4.8. PRO 140 2301 Study

PRO 140 2301 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study in 30 male and female adult subjects infected with HIV-1 [Jacobson, 2010]. Subjects were randomized to one of three groups (N=10/group), each receiving one of three treatments: (i) a single IV dose of 5 mg/kg by 30-minute IV infusion; (ii) a single IV dose of 10 mg/kg by 30-minute IV infusion; (iii) a single placebo dose by 30-minute IV infusion. The objective of the study was to assess and characterize the PK and PD of PRO 140 administered by IV infusion, assess efficacy at a new dosage level, and safety and tolerability of single doses of PRO 140.

All PRO 140-treated subjects had more than 10-fold reduction in viral loads [Jacobson, 2010]. Both the 5 mg/kg and 10 mg/kg doses have shown favorable tolerability and no dose-limiting

toxicity has been observed. High levels of receptor occupancy (>85% reduction in the number of cells detected) were observed for 29 days after treatment with both 5 and 10 mg/kg doses.

1.4.9. PRO 140 2101 Study

A subcutaneous (SC) form of PRO 140 was tested in HIV-infected subjects. The trial was a randomized, double-blind, placebo-controlled study in subjects (n=44) with early-stage, asymptomatic HIV infection, only R5 HIV-1 detectable, and no antiretroviral therapy for 12 weeks [Thompson, 2009]. Placebo (n=10) and three PRO 140 doses were examined: 162 mg weekly for three weeks (n=11), 324 mg weekly for three weeks (n=11), and 324 mg biweekly (every other week) for two doses (n=12). Subjects were followed for 44 days after the final dose.

Potent, dose-dependent and highly statistically significant antiviral activity was observed. The trial established the first antiviral proof of concept for a long-acting, self-administrable drug for HIV-1 infection [Thompson, 2009].

Subcutaneous PRO 140 was generally well tolerated both locally and systemically. There was no obvious dose-related pattern of toxicity. The most common adverse events (diarrhea, headache, lymphadenopathy and hypertension) were mild to moderate and self-resolving. These events are common in HIV infection and were reported with similar frequencies in the placebo and PRO 140 treatment groups. Administration-site reactions were mild, transient, and observed in a fraction of subjects.

1.4.10. PRO 140_CD01 Study

PRO 140_CD01 study (open-label, 43 subjects, multi-center) evaluated the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly for up to 12 weeks) for the maintenance of viral suppression following substitution of antiretroviral therapy in HIV-1 infected patients (with exclusive CCR5-tropic virus). Participants in this study were experienced HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy. Consenting patients were shifted from combination antiretroviral regimen to PRO 140 monotherapy for 12 weeks.

Forty-three (43) subjects (M/F: 37/3) with median age of 54.5 years (26-72) and median CD4 T-cell count of 604.5 cells/mm3 (365-1240) were enrolled in the CD01 study. Overall, twenty-two out of 40 (55%) enrolled subjects completed 12 weeks of PRO140 monotherapy without experiencing virologic failure. Virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days. Of the 43 enrolled subjects, 3 subjects were found to have Dual/Mixed (D/M) tropism [1 at baseline and 2 at the time of virologic failure] and 37 subjects were found to have exclusive CCR5-tropic virus. A letter of amendment was filed to increase the planned number of subjects from 40 to 43 subjects to compensate for the 3 Dual/Mixed subjects enrolled in the study.

All virologic failure subjects who had available lab data in both studies achieved viral suppression to < 400 HIV-1 RNA copies/mL, as well as viral suppression to 'Non Detectable' or < 50 HIV-1 RNA copies/mL after re-initiation of ART.

The by-subject analysis of PhenoSense® Entry Assay data for PRO140, maraviroc, and AMD3100 shows no significant changes in the post-treatment IC50 and IC90 values were noted when compared with baseline values in virologic failure and non-virologic failure groups of subjects. As the aggregate analysis shows for initial 40 subjects, the subjects who experienced virologic failure had higher IC90 value for PR0140 at baseline compared to subjects without virologic failure. The mean IC90 for subjects who experienced virologic failure was higher (10.84 µg/mL) than the IC90 for subjects without virologic failure (6.70 µg/mL) in the CD01 study (p=0.0115).

Anti-PRO140 antibodies were not identified in any post-treatment sample and data derived from the CD01 study further supports the favorable PRO140 PK profile data generated from both pre-clinical as well as prior Phase 1/2 clinical trials.

Safety data were analyzed for all 43 enrolled subjects. One (1) of 43 subjects experienced an SAE that was deemed not related to the study drug by the Principal Investigator. Twenty-eight (28) of 43 subjects (67%) experienced one or more adverse events (Aes) after receiving at least one dose of PRO140. The most commonly occurring Aes were infections and infestation conditions which were reported by 14 of 43 (32.5%) subjects. The majority of the reported Aes (62/87; 71.2%) were deemed either unlikely or not related to study treatment by the Investigator. Similarly, the majority of the reported Aes (70/87; 80.4%) were deemed mild in nature.

1.4.11. PRO 140_CD01 Extension Study

PRO 140_CD01-Extension study (open-label, 28 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy (350 mg subcutaneous injection weekly) for the continued maintenance of viral suppression following substitution of antiretroviral therapy in HIV patients (with exclusive CCR5-tropic virus). Participants in this study were HIV-infected individuals who were virologically suppressed on combination antiretroviral therapy and completed the first 12 weeks of CD01 study without experiencing virologic failure. As with the CD01 study, virologic failure was defined as two consecutive HIV-1 RNA levels of ≥ 400 copies/mL separated by at least 3 days. Consenting patients may remain on PRO 140 monotherapy until PRO 140 receives marketing approval or IND is withdrawn by Sponsor.

A total of 17 subjects participated in the CD01-Extension study of which one subject was considered not eligible as subject experienced virologic failure prior to first extension treatment.

Sixteen (16) eligible subjects (M/F: 14/2) with median age of 54.9 years (26-68) and median CD4 T-cell count of 593 cells/mm3 (365-1059) were enrolled in an extension study. One patient

discontinued at week 37 (with viral load of <40 copies/mL) due to relocation. Two subjects were withdrawn due to non-treatment related SAEs at week 140 and 149, respectively. One subject was withdrawn due to re-starting their ART at week 99. Two subjects withdrew consent at week 81 and 139, respectively. Five (5) subjects experienced virologic failure (VF) (two consecutive viral load of ≥400 copies/mL). The mean time to virologic failure was 329 days (106-691).

Five (5) subjects are currently receiving weekly 350 mg PRO140 SC monotherapy and have completed more than three years of treatment (176 – 198 weeks). Overall, 12 subjects completed at least one year of treatment and 9 subjects completed at least two years of treatment in this study

PRO140 was generally well tolerated, and no drug-related SAEs were observed.

This clinical study is currently ongoing.

1.4.12. PRO 140_CD02 Study

PRO 140_CD02 study (double blind, placebo controlled, 52 subjects, multi-center) seeks to evaluate the efficacy, safety, and tolerability of PRO 140 in combination with either existing ART (failing regimen) or Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 52 adult patients with a documented history of genotypic or phenotypic resistance to ART drugs within two or more drug classes who demonstrate evidence of HIV-1 replication despite ongoing antiretroviral therapy and have limited treatment options. The options may be limited as a result of drug antiviral class cross-resistance, documented treatment intolerance, documented objective assessments such as renal or hepatic insufficiency (e.g. high creatinine at baseline, limiting treatment options due to potential for toxicity), past adverse reactions such as hypersensitivity reactions or neuropsychiatric issues that could limit use of currently approved drugs.

In Part 1 of double-blind treatment period, virally non-suppressed subjects will be randomized and treated with either PRO 140 or Placebo in combination with the failing ART regimen for 7 days until HIV-1 genotypic drug resistance assay results are available to construct an OBT. The primary efficacy endpoint is proportion of participants with ≥ 0.5 log10 reduction in HIV-1 RNA viral load from baseline at the end of the 7 day functional monotherapy period.

In Part 2 of double-blind treatment period, subjects will continue treatment with PRO 140 in combination with OBT within the 24-week open-label period.

Fifty-two subjects with a mean age of 52.4 years, 73.1% male, 48.1% non-white and mean duration of HIV-1 infection of 20.4 years were randomized 1:1 to the PRO 140 SC or placebo arm. Subjects had been previously exposed to an average of 11 ART drugs and had documented resistance to >9 ART drugs. Mean baseline VL and CD4 cell count were 21,104 c/mL and 297.8 c/mm^3, respectively. The primary efficacy endpoint- the proportion of patients with ≥0.5 log10

reduction in HIV-1 VL from baseline at the end of the 1-week double-blind, randomized, placebo-controlled treatment period- was met (16/25 vs 6/26 [p-value <0.0032, ITT population]). Forty seven (47) of 52 patients have completed the 25-week study. Approximately 81% of patients completing 25-weeks of PRO 140 SC treatment demonstrated HIV-1 VL <50 c/mL and 92% had HIV-1 VL <400 c/mL. Continued access to PRO 140 SC was provided through a rollover study and 40 patients entered the extension protocol after completing the CD02 study. PRO 140 SC was generally well tolerated. No drug-related SAEs or treatment discontinuations were reported in the study.

This clinical study is completed pending final database lock.

1.4.13. PRO 140_CD02 Extension Study

PRO 140_CD02 Extension study (open label, 40 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 weekly injection in combination with Optimized Background Therapy (OBT) in patients infected with HIV-1. The study population includes 40 treatment-experienced HIV-infected adult patients with CCR5-tropic virus who successfully completed PRO 140_CD02 study and continue to demonstrate HIV-1 viral suppression.

This clinical study is currently ongoing.

1.4.14. PRO 140_CD03 HIV Study

PRO 140_CD03 HIV (open-label, 350 subjects, multi-center) is a three part study enrolling virally suppressed HIV-1 patients with CCR5-tropic HIV-1 receiving combination antiretroviral (cART) therapy. Patients received weekly doses of PRO 140 on single-agent maintenance therapy following one week of overlap of the existing cART regimen that is then discontinued. In part 1, 156 participants received 350 mg PRO 140 SC in a single-arm design. In part 2, 147 participants received 350 or 525 mg PRO 140 SC in a 1:1 ratio as randomized controlled, two-arm study. In an ongoing part 3, 51 participants have been randomized to receive 525 or 700 mg PRO 140 SC in a 1:1 ratio.

Despite reaching the enrollment target of 350 subjects for the PRO140_CD03 HIV study, the enrollment is ongoing as the goal of enrolling 20 subjects for the CNS sub-study have not achieved. As a result, sites that are currently participating in the CNS sub-study are permitted to continue enrollment in the CD03 HIV study.

Of the 354 patients enrolled, median age was 51 yrs (21-77) with the majority reported as male (79%) and 37% were non-white. A total of 27 subjects have been randomized to 700 mg dose. In addition, another 18 subjects have been exposed to 700 mg dose after rescuing from the lower doses (350 mg or 525mg). On average, participants were diagnosed with HIV-1 infection for 16.8 yrs and were on cART regimen for 14.8 yrs. The frequency and severity of injection site reactions

were comparable between the three dose groups (350, 525 and 700mg) and the incidence or severity of injection site reactions was not increased in patients receiving higher doses. Overall, PRO 140 SC was generally well tolerated at all dose levels in this study.

This clinical study is currently ongoing.

1.4.15. PRO 140_CD03 HIV Extension Study

PRO 140_CD03 study (open-label, 350 subjects, multi-center) seeks to evaluate the long term efficacy, safety and tolerability of PRO 140 SC as long-acting single-agent maintenance therapy in virologically suppressed subjects with CCR5-tropic HIV-1 infection. The study population includes up to 300 treatment-experienced HIV-infected adult patients who successfully completed PRO 140_CD03 HIV study and continue to demonstrate HIV-1 viral suppression.

This clinical study is currently ongoing.

1.4.16. PRO 140_CD06 Study

PRO 140_CD06 study (double-blind, 80 subjects, single-center) seeks to evaluate the evaluate comparability of PRO 140 formulation Batch Lot # 3-FIN-3143 versus formulation Batch Lot# 3-FIN-2618 as a one-time subcutaneous (SC) injection in healthy subjects under non-fasting conditions.

1.4.17. PRO 140_CD07 Study

CD07_TNBC study (open-label, two-part [Phase Ib: Up to 18 subjects; Phase II: 30 Subjects], multi-center) seeks to evaluate the efficacy, safety, tolerability and maximum tolerate dose (MTD) of leronlimab (PRO 140) when combined with carboplatin in patients with CCR5+ metastatic triple-negative breast cancer (mTNBC).

The study population includes patients with CCR5-positive, locally advanced or metastatic triple-negative breast cancer (mTNBC) who are naïve to chemotherapy in metastatic setting but have been exposed to anthracyclines and taxane in neoadjuvant and adjuvant settings (first-line).

This clinical study is currently ongoing.

1.4.18. CD08_mCRC Study

CD08_mCRC study (open-label, 30 subjects, multi-center) seeks to evaluate the effect on overall response rate (ORR) of Leronlimab (PRO 140) when combined with Regorafenib in patients with CCR5+, Microsatellite Stable (MSS), Metastatic Colorectal Cancer (mCRC).

The study population includes patients with CCR5+, Microsatellite Stable (MSS), metastatic Colorectal Cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-

and irinotecan-based chemotherapy, an antiVEGF therapy, and, if RAS wild type, an anti-EGFR therapy.

Table 1-1: List of Completed Clinical Studies with leronlimab (PRO 140)

Protocol Number	Phase	No. of Subjects (Planned/ Analyzed)	Doses	Subject Population	Comments
PRO 140 1101	1	20/20	Single 0.1, 0.5, 2.0, or 5.0 mg/kg	Healthy	Generally well tolerated; non-immunogenic; dose-dependent coating of CCR5; significant coating of CCR5 over placebo at 0.5, 2, and 5 mg/kg
PRO 140 1102	1	20/20	Either two or three doses totaling 200 or 350 mg respectively	Healthy	Generally well tolerated; drug derived from CHO cells well tolerated also; SC administration by Autoject® 2 better tolerated than manual injection
PRO 140 1103	1	15/14	Two doses, each of 350 mg	Healthy	More Aes associated with arm injection; trend of lower exposure in arm injections; thigh and abdominal administration preferred
PRO 140 1302	1b	40/39	Single 0.5, 2.0, or 5.0 mg/kg	HIV-1 positive	Generally well tolerated; antiviral suppression maintained for approx. 10 days with higher doses; favorable tolerability and potent, dose-dependent antiviral activity provide proof-of-concept
PRO 140 2301	2a	30/31	Single 5.0 or 10.0 mg/kg	HIV-1 positive	Generally well tolerated with no dose-limiting toxicities; potent antiviral suppression maintained for approx. 20 days when administered IV at 5 or 10 mg/kg. No dose-limiting toxicities at 10 mg/kg.
PRO 140 2101	2a	40/44	Three doses of 162 or 324 mg each	HIV-1 positive	Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; antiviral activity was statistically significant; two-fold exposure at higher dose; single dose demonstrated favorable tolerability, and potent, long-acting, dose-dependent antiviral activity.
PRO 140 CD01	2b	43/43	350 mg SC weekly dose for	HIV-1 positive	Generally well tolerated, no drug-related SAEs or dose-limiting toxicity; Open-label

Protocol Number	Phase	No. of Subjects (Planned/ Analyzed)	Doses	Subject Population	Comments
			12 weeks of monotherapy (total treatment duration 14 weeks)		administration of PRO 140 demonstrated favorable tolerability, and potent, long-acting, antiviral activity.
PRO 140 CD02	2b/3	50/52	350 mg SC weekly dose of PRO 140 or placebo along with existing ART for 1 week then PRO 140 along with optimized background therapy for 24 weeks (total treatment duration 25 weeks)	HIV-1 positive, treatment-experienced	This study is completed pending database lock.
PRO 140 CD06	PK	80/79	Single dose PK study with 350 mg SC dose	Healthy	This clinical study is completed.

Table 1-2: List of Ongoing Clinical Studies with leronlimab (PRO 140)

Protocol Number	Phase	No. of Subjects (Planned/ To be analyzed)	Doses	Subject Population	Comments
PRO 140 CD_01-Extension	2b	17/16	350 mg SC weekly dose (as monotherapy)	HIV-1 positive, treatment experienced	This clinical study is currently ongoing.
PRO 140 CD02 Extension	2b/3	50/40	350 mg SC weekly dose in combination with Optimized Background Therapy (OBT)	HIV-1 positive, treatment experienced	This clinical study is currently ongoing.

Protocol Number	Phase	No. of Subjects (Planned/ To be analyzed)	Doses	Subject Population	Comments
PRO 140 CD03	2	350/TBD	350 or 525 or 700 mg SC weekly dose for 46 weeks of monotherapy (total treatment duration 48 weeks)	HIV-1 positive, treatment-experienced	This clinical study is currently ongoing.
PRO 140 CD03 Extension	2	350/TBD	350 or 525 or 700 mg SC weekly dose (as monotherapy)	HIV-1 positive, treatment experienced	This clinical study is currently ongoing.
PRO 140 CD07	1a/2b	Phase Ib: Up to 18 subjects Phase II: 30 Subjects	350 or 525 or 700 mg SC weekly dose in combination with carboplatin	Triple negative breast cancer	This clinical study is currently ongoing.
CD08_mCRC	2	30/TBD	700 mg SC weekly dose in combination with Regorafenib	CCR5+, Microsatellite Stable (MSS), Metastatic Colorectal Cancer (mCRC).	This clinical study is pending start-up.
CD09_Basket	2	30/TBD	350 or 525 or 700 mg SC weekly dose	Solid tumors	This clinical study is pending start-up.

1.5 STUDY RATIONALE

1.5.1. Rationale for Target Population

Triple-negative breast cancer (TNBC), defined clinically as tumors that do not express estrogen receptors (ER), progesterone receptors (PgR), or HER-2, remains a major therapeutic challenge due to the lack of available targeted agents and the high risk of disease recurrence [Dawood, 2011][Engstrom, 2013]. Although anthracyclines and taxanes are the most active agents, most will require other chemotherapy options. TNBC is associated with a higher incidence of visceral metastasis as site of first-recurrence compared to other disease subtypes. Following recurrence, TNBC patients fare less well than their non-TNBC counterparts, with a median response duration to first-line palliative therapy of only 3 month, a median PFS of 5 months and a median survival of 9–12 months [Dawood, 2011][Harbeck, 2016][Malorni, 2012]. PFS has been considered an

adequate endpoint in this population when evaluating the role of biological agents including PARP-inhibitors and antiangiogenic agents such as bevacizumab.

Metastasis is the primary cause of death in patients with breast cancer. Currently no treatments exist that are directed specifically to the metastatic process. The current proposal provides strong preliminary evidence that: 1) a receptor, CCR5, is expressed in a subset of human breast cancer, 2) CCR5 is intrinsically related to invasiveness and metastasis cascade, 3) CCR5 is associated with upregulation of PD-L1 and the adaptative immune system process of tumor evasion, 4) CCR5 correlates with DNA repair activities. Furthermore, CCR5 inhibitors, previously developed and FDA approved fortreatment of HIV patients, can effectively block breast cancer metastasis in preclinical models. The repurposing of drugs for alternative use in cancer metastasis, drugs that were previously approved by the FDA, may provide a more rapid solution for this deadly disease.

1.5.2. Rationale for Dose Selection

Leronlimab (PRO 140) is currently under development for the indication of HIV in combination with other antiretroviral agents or as single agent maintenance therapy for the treatment of only CCR5-tropic human immunodeficiency virus type 1 (HIV-1) infection. The safety profile of leronlimab (PRO 140) has been extensively evaluated in clinical trials of HIV-positive patients. PRO 140 has been administered intravenously or subcutaneously to more than 750 healthy and HIV-1 infected individuals in Phase I/II/III studies. The drug has been well tolerated following intravenous administration of single (or multiple) doses of 0.5 to 10 mg/kg or up to 700 mg weekly doses as subcutaneous (SC) injection. Overall, 324 subjects have been exposed to PRO 140 350 mg SC weekly dose with the longest duration of exposure lasting 4 years. Similarly, more than 250 and 150 subjects have been exposed to PRO 140 525 mg and 700 mg SC weekly dose, respectively. No dose-proportional increases in incidence and severity of AEs were reported at the 700 mg dose compared to the 525 mg and 350 mg dose levels of PRO 140 (leronlimab).

We anticipate a manageable safety profile with combination therapy since: 1) Leronlimab (PRO 140) is not metabolized by the liver, and therefore may have the potential for a better tolerability profile than many of the existing small-molecule therapies; 2) Unlike small molecules, monoclonal antibodies are too large to be filtered by the kidneys and are not eliminated in the urine, except in pathologic conditions. If low molecular weight antibody fragments are filtered, they are usually reabsorbed and metabolized in the proximal tubule of the nephron. These pharmacodynamic characteristics and current safety profile led to the selection of 350 mg of leronlimab (PRO 140) as the starting dose in combination with other chemotherapy agents.

Once the maximum tolerated dose (MTD) has been established/reached under the ongoing dose-escalation study of Leronlimab in combination with carboplatin in patients with Metastatic Triple-Negative Breast Cancer (CD07 TNBC Study), the dose of Leronlimab given in combination with other chemotherapy agents will be modified accordingly for this CD07 TNBC Compassionate-Use Study.

Note: Based on successful safety data review for the first three subjects enrolled in CD07_TNBC Study in Cohort A (350 mg leronlimab SC weekly + AUC 5 Carboplatin every 3 weeks), dose escalation to proceed with enrollment of subjects under Cohort B (525 mg leronlimab SC weekly + AUC 5 Carboplatin every 3 weeks). The similar dose change of Leronlimab in combination with other chemotherapy agents is now implemented under the current protocol version for the CD07 TNBC Compassionate-Use Study.

1.6 RISKS / BENEFITS ASSESSMENT

1.6.1. Risks/Discomfort to Subjects and Precautions to Minimize Risk

Allergic Reaction

Leronlimab (PRO 140) belongs to the monoclonal antibody class of drugs. Monoclonal antibodies are sometimes associated with allergic reactions or flu-like reactions (such as fever, chills, and aches) or injection-site reactions. These events are usually of short duration if they occur at all. Severe allergic reactions, however, can be life-threatening. Although anaphylaxis has not been observed in prior trials of leronlimab (PRO 140), infusion of proteins always carries with it the theoretical risk for anaphylactic shock. Accordingly, whenever leronlimab (PRO 140) is administered to subjects, there should be available and in place the procedures required to manage anaphylactic shock.

Immune Response

People who take leronlimab (PRO 140) or other monoclonal antibodies can also develop an immune response to leronlimab (PRO 140) that may affect their ability to receive monoclonal antibodies, or to benefit from diagnosis or therapy with a monoclonal antibody in the future.

Pregnancy

Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. Females of childbearing potential must have a negative pregnancy test prior to enrollment. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized).

Venipuncture

Blood sampling is required as part of the study protocol. Blood sampling carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection at the needle puncture site.

Core or excisional biopsy

A core or excisional biopsy may be necessary in order to evaluate the CCR5 receptor status of the breast cancer tumor 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. Serious complications related to core biopsy are rare. The commonest problem is bleeding, which is usually easy to control at the time of the procedure. Rarer complications of core biopsy include infection and abscess formation, pneumothorax, milk fistula formation, cosmetic deformity and seeding of tumor along the biopsy track. Compared to a needle biopsy, a surgical biopsy is more invasive, has a longer, more uncomfortable recovery time and has a higher risk of infection and bruising.

Unknown Risks

As with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

Theoretical risk for increased severity of West Nile virus infection

Individuals who lack a functional CCR5 gene are at increased risk for severe infection by West Nile virus [Thompson, 2009]. Because of this, treatment with CCR5 co-receptor antagonists poses a theoretical risk for increased severity of West Nile virus infection. However, this concern is mitigated by several factors. First, no increased risk was observed for individuals who possess one functional and one non-functional CCR5 gene, indicating that an intermediate amount of CCR5 is sufficient for defense against West Nile virus [Thompson, 2009]. Second, use of CCR5 co-receptor antagonists is unlikely to completely abrogate CCR5 function, and there has been no association reported to date between CCR5 co-receptor use and severe West Nile virus. Additionally, leronlimab (PRO 140) weakly antagonizes the natural activity of CCR5 and thus is less likely to adversely affect immune function. However, patients enrolled in this study may have immune suppression from chemotherapy and therefore, DSMB and the investigators will be alerted to risks of West Nile infections. Furthermore, this has not been established to be a risk with maraviroc, the other FDA-approved anti-CCR5 drug already.

Collectively, the experience with both IV and SC, simulation modeling and the recent confirmation that a higher concentration of leronlimab (PRO 140) synthesized using a highly efficient CHO cell line can be conveniently and safely administered has resulted in the design of the current study.

1.6.2. Intended Benefit for Subjects

This study provides an opportunity for subjects with CCR5 + metastatic triple negative breast cancer previously treated in neoadjuvant and adjuvant settings to have once weekly SC treatment

with leronlimab (PRO 140) in combination with treatment of physician's choice (TPC). Subjects participating in the present study will contribute to the development of a drug which has the potential to become a treatment option for them and others in the future.

2 STUDY OBJECTIVES

Primary Objective:

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 Objectives:

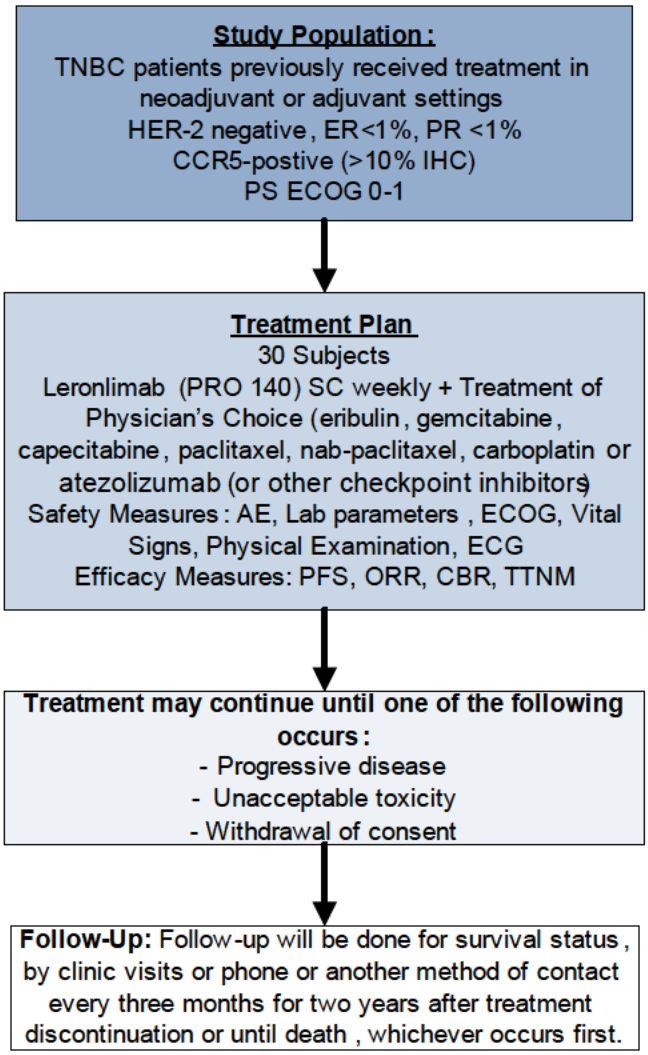
The secondary objective of this study is to collect further safety, tolerability and efficacy data.

To evaluate correlative studies for better treatment selection in future validation studies

3 STUDY DESIGN

This is a multicenter study that will enroll up to 30 subjects. The target population for this study is subjects with histologically confirmed diagnosis of CCR5 positive, metastatic triple-negative breast cancer (documented by HER-2 negative, ER<1%, PR<1%). A study flow schematic is presented in Figure 3-1~~Figure 3-1~~.

Figure 3-1: Study Schematic



Note: 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 .

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 525 mg until disease progression or intolerable toxicity. Treatment of Physician's Choice (TPC) is defined as the following drugs administrated according to local practice: eribulin, gemcitabine, capecitabine, paclitaxel, nab-paclitaxel, carboplatin, or atezolizumab (or other checkpoint inhibitors). The selected treatment should be administered as per the dosing schedule included on the package insert.

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.

Note: Subjects participating under Protocol version 1.0 – 3.0 received 350 mg of PRO 140. Dose was increased from 350 mg to 525 mg weekly under version 4.0 of this protocol.

Subjects enrolled under previous versions of the protocol have the option of remaining on their current dose of 350mg or increasing their dose to 525 mg for the remainder of the trial.

3.1 STUDY CENTER

Up to 10 centers in the United States (US).

3.2 STUDY POPULATION

The target population for this study is subjects with histologically confirmed mTNBC that express CCR5 (> 10% membranous staining completed at the laboratory at the Medical College of Wisconsin).

This will be a multicenter trial. A total of 30 subjects will be needed for this trial.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study.

3.3 ELIGIBILITY CRITERIA

3.3.1. Inclusion Criteria

Subjects are required to meet all of the following criteria for enrollment into the study:

1. Must have a histologically confirmed diagnosis of TNBC. Must demonstrate HER-2 negative (IHC 0, 1+, or fluorescence in situ hybridization (FISH) negative and ER< 1%, and PR < 1%, per ASCO/CAP criteria);

   Note: Patients with ER and/or PR <10% who have failed on endocrine therapy will also be eligible for participation in the study.

2. Demonstrate CCR5 + by IHC (>10% of primary or metastatic tumor cells shows membranous staining and/or high predominance of CCR5+ tumor-infiltrating leukocytes completed at the reference laboratory of Dr. Hallgeir Rui at Medical College of Wisconsin).

   Note: This test will be done as part of the pre-screening period. It will be performed in archival metastatic tissue. If archival tissue is not available then, fresh biopsy will be done;

3. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion (in case archival tissue is not available);

4. Patients with de novo (metastatic or stage IV at initial diagnosis) breast cancer OR Patients with locally recurrent or metastatic breast cancer who have been treated up to 3 previous line of systemic therapies (including neo/adjuvant setting) and had progressed or were intolerant to the latesttreatment.

   Note: Patients with PDL-1+ that elect not to receive checkpoint inhibitor or are excluded for medical conditions will be eligible for participation in the study.

5. Patients must have measurable disease based on RECIST v1.1;

6. Female patients, ≥ 18 years of age;

7. Patients must exhibit a/an ECOG performance status of 0-1;

8. Life expectancy of at least 6 months;

9. Patients must have adequate organ and bone marrow function within 28 days prior to registration, as defined below:

   - leukocytes ≥ 3,000/mcL;
   - absolute neutrophil count ≥ 1,500/mcL;
   - platelets ≥ 100,000/mcL;
   - total bilirubin: within normal institutional limits;
   - AST(SGOT) &ALT(SPGT) ≤ 2.5 X institutional upper limit of normal (ULN) (applicable to all patients, irrespective of liver disease or metastasis); and

- creatinine: within normal institutional limits.

10. Clinically normal resting 12-lead ECG at Screening Visit or, if abnormal, considered not clinically significant by the Principal Investigator.
11. Females of child-bearing potential (FOCBP) and males must agree to use two medically accepted methods of contraception with hormonal or barrier method of birth control, or abstinence, prior to study entry, for the duration of study participation and for 60 days after the last dose of study drug (Refer to Appendix 1). Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. NOTE: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
    - Has not undergone a hysterectomy or bilateral oophorectomy; and
    - Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months).
12. FOCBP must have a negative serum pregnancy test at Screening Visit and negative urine pregnancy test prior to receiving the first dose of study drug; and
13. Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.3.2. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from enrollment:

1. HER-2 overexpressed/amplified MBC (Appendix 2 for guidelines from ASCO);
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 28 days prior to enrollment;
3. Patients who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to leronlimab (PRO 140) are not eligible;
4. Patients who have had prior exposure to CCR5 antagonists are not eligible;
5. Patients who have a known additional malignancy that is progressing or requires active treatment are not eligible. Patients who have had a prior diagnosis of cancer and if it has been <3 years since their last treatment are not eligible. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer;

6. Has an active infection requiring systemic therapy. Note: Patients must complete any treatment with antibiotics prior to registration;
7. Patients who have a known HIV positive status or known/ active Hepatitis B and/or C infection are not eligible;
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability;
9. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator;
10. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial; and
11. Is pregnant or breastfeeding, or expecting to conceive or have children within the projected duration of the trial, starting with the pre-screening or screening visit through the duration of study participation.

4 STUDY SCHEDULE

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~~Figure 4-1~~.

- **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.
- **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.
- **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 treatment until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent.
- **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.

Figure 4-1: Study Flow Diagram

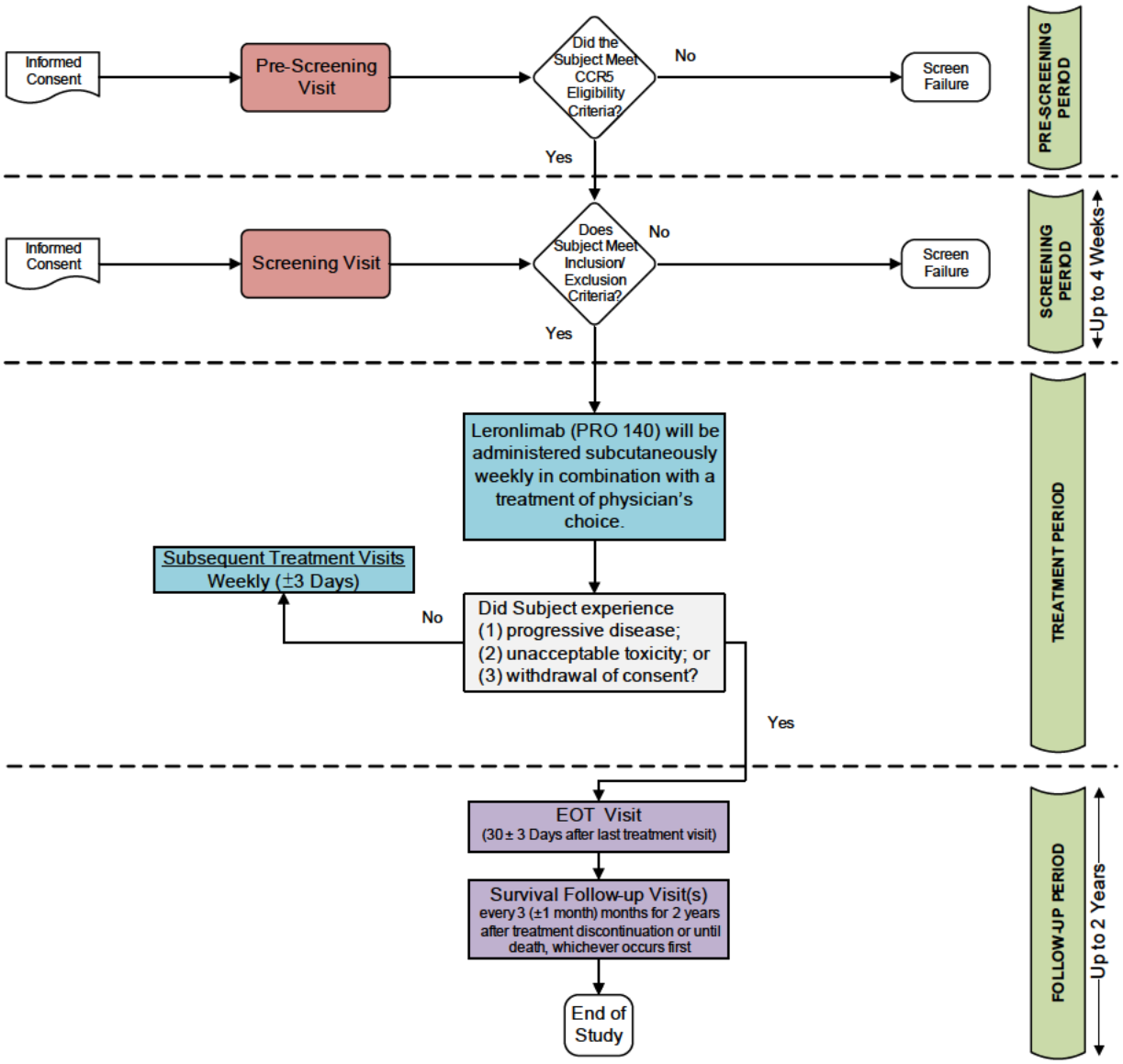


Table 4-1: Schedule of Assessments

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 X		30 Days (±3) after last treatment visit	Every 3 months [20]
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[21]	X[22]
Tumor Imaging Assessment [8]		X																	X[22]
Complete Blood Count [9][27]		X	X[24]			X[24]			X[24]			X[24]			X[24]			X	
Biochemistry [10][27]		X	X[24]			X[24]			X[24]			X[24]			X[24]			X	
Urinalysis [11][27]		X	X[24]			X[24]			X[24]			X[24]			X[24]			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 CTCs PD-L1 /CCR5 Analysis [13]			X			X			X			X			X			X	
Blood sample collection for			X			X			X			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 X		30 Days (±3) after last treatment visit	Every 3 months [20]
Window			±3 days since last treatment																
CTC and CAMLs Analysis [14]																			
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			
Post Injection Site Evaluation by Investigator [18]			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			
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	X[23]
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.

[3] 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 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 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 525 mg (175 mg/mL) is delivered as two injections of 1.5 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~~7.17~~

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

[27] 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).

4.1 PRE-SCREENING PERIOD

4.1.1. Pre-Screening Visit

Sites are required to pre-screen subjects for study inclusion, evaluating CCR5 positive status by Immunohistochemistry (IHC) assay prior to performing a full screening visit. 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 obtained.

The subject will sign and date the pre-screening informed consent form (ICF) in-person or remotely prior to any study-related pre-screening procedures. The remote consenting will involve the site sending the pre-screening ICF to subject (via hard copy or email) to discuss the consent over the phone. The written informed consent must be signed and personally dated by the subject, sent back to the site and will then be signed by the person who conducted the informed consent discussion. The consent process and discussion over the phone will be captured in the medical records.

A unique identification number will be assigned to each subject who has provided written pre-screening informed consent. The subject unique identification number will incorporate a three-digit Study Center number (751, 752 or 753….) and a three-digit numeric ID assigned in successive order of entering the study after signing the pre-screening ICF at each center, beginning with 001 at each site (e.g. 751-001 or 752-001).

Subject Screening # : **XXX - YYY**

XXX=Study Center YYY=Subject Numeric ID

Once the pre-screening ICF has been signed, the following procedures and information will be obtained to confirm pre- eligibility including:

- Review of prior medical records
- CCR5+ status confirmed by archival or fresh biopsy from primary or metastatic site
- Breast tissue sample collected (primary or metastatic) for PD-L1 expression level

A pre-screening log will be maintained to capture the following information:

- Subject unique identification number
- Patient initials
- Date pre-screened
- Initial eligibility

- Date of re-consent (for the full consent form) or reason for ineligibility

4.2 SCREENING PERIOD

4.2.1. Screening Visit (SV)

The subject (or Legally Acceptable Representative (LAR)) will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. All study centers will be instructed to maintain the study-specific screening and enrollment logs at their sites. If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new unique identification number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

Once the Screening ICF has been signed, screening procedures and information will be obtained to confirm subject eligibility including:

- Demographic information and baseline disease characteristics (see Section 7.3~~7.3~~),
- Medical history (see Section 7.4~~7.4~~),
- Prior medications assessment (see Section 7.5~~7.5~~),
- Vital Signs (see Section 7.6~~7.6~~),
- Body Weight & Height measurements (see Section 7.6),
- Physical examination (see Section 7.7~~7.7~~),
- Eastern Cooperative Oncology Group (ECOG) Performance Review (see Section 7.8~~7.8~~)
- 12-lead Electrocardiogram (see Section 7.9~~7.9~~)
- Tumor imaging assessment (see Section 7.15~~7.15~~)

  Note: Prior imaging assessment within the last 3 months of the Screening Visit is acceptable

- Collection of lab specimens (see Section 7.11~~7.11~~) for
  - Complete blood count
  - Biochemistry
  - Serum pregnancy test, for female subjects of childbearing potential.

- Urine sample for urinalysis parameters

All screening information will be fully documented in the subject's medical records (i.e., source documents).

- For consented subjects who do not meet eligibility criteria, a Screen Failure Case Report Form (CRF) will be completed. The Screen Failure CRF will contain the following details: the subject identification number, the date of ICF signature, demographic information (see Section 7.3~~7.3~~), and the reason for screen failure. No additional information will be required for subjects who fail screening.
- For consented subjects who meet eligibility criteria, all required screening information will be transcribed onto the appropriate page of the CRF.

4.3 TREATMENT PERIOD

Subjects who meet all eligibility criteria, as per data gathered from Screening Period are to be treated. All subjects who fail to meet eligibility criteria will be considered screen failure and exit the study without further evaluation

The maximum sample size for this study is 30 subjects that will be followed by treatment according to the schedule described above starting at Treatment Visit 1 (Week 1).

Treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), or
- Withdrawal of consent

4.3.1. Treatment Period, T1 (Week 1)

The following assessments will be performed at the first treatment visit of the treatment period:

- Concomitant medications assessment (see Section 7.5~~7.5~~),
- Vital Signs and body weight measurement (see Section 7.6~~7.6~~),
- Physical examination, including evaluation of all body systems (see Section 7.7~~7.7~~)
- ECOG Performance Status (see Section 7.8~~7.8~~)
- 12-lead Electrocardiogram (see Section 7.9~~7.9~~)
- Collection of lab specimens (see Section 7.11~~7.11~~) for

- Complete blood count
- Biochemistry
- Urine pregnancy test, for female subjects of childbearing potential.
- Urine sample for urinalysis parameters
- CTCs PD-L1/CCR5 analysis
- CTC and CAMLs analysis

- **Note:** Complete blood count, biochemistry and urinalysis can be performed within 3 days prior to each visit.
- Leronlimab (PRO 140) Administration (see Section 6.1.3~~6.1.3~~)
- Post Injection Site Evaluation (performed by Investigator) (see Section 7.13~~7.13~~)
- Toxicity assessment (see Section 7.10~~7.10~~) and Review of Adverse Events (see Section 9~~9~~)
- Treatment of Physician's Choice (See Section 7.17~~7.17~~)

4.3.2. Treatment Period, T2 (Week 2) Onward

The following assessments will be performed at during the remaining visits during the treatment period:

- Concomitant medications assessment (see Section 7.5~~7.5~~),
- Vital Signs (see Section 7.6~~7.6~~),
- Body weight measurement on T4, T7, T10, and every 3 weeks after (see Section 7.6~~7.6~~),
- Physical examination, including evaluation of all body systems on T4, T7, T10, and every 3 weeks after (see Section 7.7~~7.7~~)
- ECOG Performance Status on T4, T7, T10, and every 3 weeks after (see Section 7.8~~7.8~~)
- Collection of lab specimens (see Section 7.11~~7.11~~) for
  - Complete blood count
  - Biochemistry
  - Urine pregnancy test, for female subjects of childbearing potential on T4, T7, T10, and every 3 weeks after.
  - Urine sample for urinalysis parameters
  - CTCs PD-L1/CCR5 analysis on T4, T7, T10, and every 3 weeks after

- CTC and CAMLs analysis on T4, T7, T10, and every 3 weeks after

- **Note:** Complete blood count, biochemistry and urinalysis can be performed within 3 days prior to each visit.
- Leronlimab (PRO 140) Administration (see Section 6.1.3~~6.1.3~~)
- Post Injection Site Evaluation (performed by Investigator) (see Section 7.13~~7.13~~)
- Toxicity assessment (see Section 7.10~~7.10~~) and Review of Adverse Events (see Section 9~~9~~)
- Treatment of Physician's Choice (See Section 7.17~~7.17~~)

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

4.4 FOLLOW-UP PERIOD

Duration of Follow Up

- 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)).
- All patients will be followed for adverse events for 30 days after last dose of leronlimab (PRO 140) or until the patient starts a new treatment, whichever occurs first.
- 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.
- 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.

4.4.1. End of Treatment Visit (EOT)

An EOT visit will take place 30 (± 3) days from the last treatment visit.

The following assessments will be performed at the EOT visit:

- Concomitant medications assessment (see Section 7.5~~7.5~~),

- Review of Adverse Events (see Section 99)
- Vital Signs (see Section 7.67.6),
- Physical examination, including evaluation of all body systems (see Section 7.77.7),
- ECOG Performance Status (see Section 7.87.8),
- 12-lead Electrocardiogram (see Section 7.97.9),
- Toxicity Assessment (see Section 7.107.10),
- Collection of lab specimens (see Section 7.117.11) for
    - Complete blood count
    - Biochemistry
    - Urine sample for urinalysis parameters
    - CTCs PD-L1/CCR5 Analysis
    - CTC and CAMLs Analysis
- Survival status (see Section 7.167.16)

4.4.2. Survival Follow-up Visits

Survival follow-up visits will be performed every 3 months (±1 month) for 2 years after treatment discontinuation or until death, whichever occurs first. Subjects will be followed up by clinic visits or phone call or another method of contact, for survival status. During the visit, the following assessments will be performed:

- Survival status
- Concomitant medications (limited to all subsequent anti-cancer treatments)
- Toxicity assessment

  Note: *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).*

- Tumor imaging assessment (see Section 7.157.15 and note below)

  Note: *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.

4.5 UNSCHEDULED VISITS

In the event that the subject will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the eCRF.

Any hospitalization or ER visits in between the scheduled visits should be promptly notified to the site staff.

5 SUBJECT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

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.

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Reasonable effort will be made to determine why any subject withdraws from the study prematurely. This information will be recorded. If a subject withdraws prematurely after dosing, subjects will be monitored until they are stable for discharge from the clinic. All data normally collected at the scheduled Post-Study (Follow-up) Visit should be recorded at the time of premature discontinuation.

5.1 REMOVAL OF SUBJECTS FROM STUDY TREATMENT AND/OR STUDY AS A WHOLE

Subjects can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Subject voluntarily withdraws from treatment (follow-up permitted)
- Subject withdraws consent (no follow-up permitted)
- Subject is unable to comply with protocol requirements
- Subject demonstrates disease progression
- Subject experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the subject's best interest
- Subject becomes pregnant
- Subject develops a second malignancy that requires treatment which would interfere with this study
- Subject becomes lost to follow-up (LTF)

If a subject fails to return for the scheduled study visit or is discontinued from the study, an attempt will be made to determine the reason(s). If the subject is unreachable by telephone, a registered letter will be sent to the subject requesting that he/she contact the clinic.

All patients with an ongoing SAE at the Post-Study (Follow-up) Visit (scheduled or premature) must be followed until the event is resolved (with or without sequelae) or deemed stable.

5.2 DATA COLLECTED FROM WITHDRAWN SUBJECTS

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and on the appropriate page of the CRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one certified letter.

In the event that a subject is withdrawn from the study at any time due to an adverse event or SAE, the procedures stated in Sections 9.29.2 and 9.49.4 must be followed.

5.3 SCREEN FAILURES

A subject who signed a consent form, but did not meet the inclusion/exclusion criteria is classified as a screen failure. Subject number, demographics and reason for screen failure will be recorded.

In the event that a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened again (i.e., up to two screenings) and may be enrolled if they are found to meet all inclusion and no exclusion criteria at the subsequent screening visit.

6 STUDY TREATMENT

Eligible subjects will receive leronlimab (PRO 140) in combination with a treatment of physician's choice. Leronlimab (PRO 140) will be administered weekly at a dose of 525 mg SC until disease progression or intolerable toxicity.

Table 6-1: Treatment Administration Summary

Study Drug	Premedication	Dose	Route	Schedule	Supportive Therapies
Leronlimab (PRO 140)	N/A	525 mg	SC	Start on Week 1 and every week thereafter	N/A

Supportive care: Any required supportive care treatment such as antibiotics, anti- emetics, proton pump inhibitors and others will be given per institutional standards.

6.1 LERONLIMAB (PRO 140)

Leronlimab (PRO 140) is a humanized IgG4,κ monoclonal antibody (mAb) to the chemokine receptor CCR5. Leronlimab (PRO 140) is provided at a concentration of 175 mg/mL and is intended for SC route of administration.

A total 525 mg of leronlimab (PRO 140) (175 mg/mL) is delivered as two injections of 1.5 mL (or one injection of 3 mL) administered subcutaneously on opposite sides of the abdomen.

One study injection kit will be assigned per subject per treatment visit. Kits will be labeled with a unique identification number. Each kit used during the Treatment Period will contain three vials of leronlimab (PRO 140) for SC injection.

Each vial of the leronlimab (PRO 140) product contains ~1.4 mL antibody at 175mg/mL in a buffer containing 5 mM L-histidine, 15.0 mM glycine, 95 mM sodium chloride, 0.3% (w/v) sorbitol, 0.005% (w/v) polysorbate 20 (Tween 20®), and sterile water for injection, at pH of 5.5.

Note: *1 mL will be drawn from 1.4 mL solution in a vial. Remaining 0.4 mL medication will be discarded appropriately from each vial.*

Table 6-2: Investigational Product - leronlimab (PRO 140)

IP Dosage	Dosage Form	IP concentration	Dosing Frequency and Amount	Route of Administration
PRO 140 525 mg	Parenteral solution	175 mg/mL	2 injections of PRO 140 (1.5 mL/inj.) per week on opposite sides of abdomen	SC injection

6.1.1. Leronlimab (PRO 140) - Packaging and Labeling

Study drug will be prepared by Ajinomoto Althea, Inc. and will be packaged, labeled, and shipped by PCI Pharma Services.

The contents of each vial are described in Section 6.16.1. Leronlimab (PRO 140) kits will be labeled with information such as: study protocol #; fill volume; concentration; storage condition; a "use as per study protocol" statement; a cautionary statement; sponsor's name and address; and the kit number.

Below are representative samples of the Investigational Product, FDP individual vial (Figure 6-1~~Figure 6-1~~), syringe label (Figure 6-2~~Figure 6-2~~), and kit labels (Figure 6-3~~Figure 6-3~~) designated for use in this clinical protocol. Each kit contains two labeled vials and two syringe labels.

Figure 6-1: Investigational Product - Vial Label

Protocol: PRO 140_CD07_Compassionate Use Kit No. xx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection Store at 2ºC to 8ºC (36ºF to 46ºF) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA	Protocol: PRO 140_CD07_Compassionate Use Kit No. xx Subject No. _____ Single use 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection Store at 2ºC to 8ºC (36ºF to 46ºF) USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

Figure 6-2: Investigational Product - Syringe Label

Protocol: PRO 140_CD07_Compassionate Use Contents of Kit No. xxx This syringe contains 1.5 mL PRO 140 (175 mg/mL) solution for subcutaneous injection USE AS PER STUDY PROTOCOL Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use CytoDyn Inc., Vancouver, WA, USA

Figure 6-3: Investigational Product - Kit Label

Protocol: PRO 140_CD07_Compassionate Use Kit No. xxx

Site No. _____ Subject No. _____

This kit contains XX single-use vials

Each 3 mL vial contains 1.4 mL of PRO 140 (175 mg/mL) solution for subcutaneous injection

Store at 2°C to 8°C (36°F to 46°F)

USE AS PER STUDY PROTOCOL

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

CytoDyn Inc., Vancouver, WA, USA

The pharmacy manual provides the criteria regarding vial acceptance or rejection, as well as instructions for the preparation of the IP syringes to be used to administer drug.

6.1.2. Leronlimab (PRO 140) - Storage and Handling

Study drug will be shipped at 2°C to 8°C (refrigerated [36°F to 46°F]) to the investigator's site. Upon receipt at the site, the responsible site staff or pharmacist should verify the integrity of the vials. Study drug should be stored at 2°C to 8°C (refrigerated [36°F to 46°F]). The contents of the vial should appear as a clear to opalescent, colorless to yellow solution; fine translucent particles may be present. This is normal.

The investigator must maintain an accurate record of the shipment, storage, and dispensing of the study drug in a drug accountability log. An accurate record including the date and amount of study drug dispensed to each subject must be available for inspection at any time. A study CRA assigned to monitor the investigational site will review these documents once study drug has been received by the investigational site. Study drug will be accounted for on an ongoing basis during the study.

6.1.3. Leronlimab (PRO 140) - Administration

Guidelines for dose preparation can be found in the pharmacy manual.

Leronlimab (PRO 140) will be provided to the administering personnel in single-use syringes prepared from vials of study drug stored at 2-8°C at the site pharmacy prior to use. Each of two syringes is filled to deliver 1 mL of study drug (per assigned dose).

Equivalent volumes of leronlimab (PRO 140) will be administered subcutaneously on opposite sides of the abdomen.

A 20-guage needle should be used to remove leronlimab (PRO 140) from vial and a 25-guage needle is used for administration to subjects.

IP should be administered slowly over 15 seconds per mL. Leronlimab (PRO 140) should not be kept in syringe for longer than 60 minutes.

Following each SC delivery of drug, careful examination will be made to assess the appearance of any study drug Injection Site Reactions (ISRs) as per CTCAE v5.0

- All doses of study drug will be prepared by either the credentialed pharmacist or qualified medical professional and will be administered as SC injection by a licensed medical professional when leronlimab (PRO 140) is administered at clinic site. Self administration by subjects at home is allowed at certain visits.
- All initial leronlimab (PRO 140) SC weekly injections a 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.

Note: It is preferred that the same injection site be used throughout the study. At the same time, it is not recommended to inject the study drug into areas where skin shows signs of a previous injection site reaction. It is advised to change the injection site if any previous injection site reaction remains unresolved.

6.1.4. Leronlimab (PRO 140) - Post Injection Monitoring

Subject will be observed at approximately 30 minutes post-injection or longer if necessary for injection site reaction as per CTCAE v5.0.

In addition, the tolerability of repeated subcutaneous administration of leronlimab (PRO 140) is evaluated based on assessment of subject-perceived injection site pain using the Pain Visual Analog Scale (VAS).

6.1.5. Leronlimab (PRO 140) - Dose Modifications

The dose interruption and permanent discontinuation for any toxicity are described below.

Dose interruption: Refer to Table 6-3~~Table 6-3~~ below. Recovery to acceptable levels must occur to allow leronlimab (PRO 140) continuation. Any adverse event deemed to be related to

leronlimab (PRO 140) that requires a dose hold of more than 21 days will result in permanent discontinuation of leronlimab (PRO 140).

Table 6-3: Leronlimab (PRO 140) Dose Modification and Management for Injection Site Reactions

CTCAE Grade	Treatment Modifications
Grade 1	No dose adjustment is required.
Grade 2	First Occurrence: No dose adjustment is required. Second Occurrence of the same event: Closely follow-up for resolution of the AE to Grade ≤ 1
Grade 3	Withhold treatment until symptoms resolve to: • Grade 1 or less
Grade 4	Study treatment will be permanently discontinued

Permanent discontinuation of Treatment: If toxicity is reported at 525mg dose.

6.1.6. Leronlimab (PRO 140) - Disposition

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels or any partially used or unused drug supply until instructed by the Sponsor. At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused drug containers and drug labels to the drug distributor as directed by the Sponsor. A copy of the completed drug disposition form will be sent to CytoDyn, Inc. or to its designee.

6.1.7. Leronlimab (PRO 140) - Accountability

Study drug must be used in accordance with this protocol and only under the direction of the responsible investigator. The investigational site must maintain complete and accurate records showing receipt and disposition of all study drug, including master records listing the date of receipt, the number and nature of medication units received, and a dispensing record which includes each quantity dispensed, identification of the staff member/subject to whom dispensed, the date of dispensing, the intended study participant, and the identification of the preparer. All used and unused study kits will be retained by the investigational site until drug accountability can be confirmed by study CRA during the monitoring visits. Instructions will be provided by Sponsor regarding final disposition of all study drug in compliance with applicable regulations.

6.1.8. Return and Retention of Study Drug

All unused investigational products will be disposed of according to the investigational site policy for standard of care drugs.

7 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1 INFORMED CONSENT

A written informed consent will be obtained for this study for pre-screening and screening by the Investigator or designee from all subjects prior to performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

The Investigator must comply with applicable regulatory requirements and must adhere to the Good Clinical Practice (GCP) in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform subjects of all pertinent aspects of the study. Before written informed consent is obtained from the subject, the Investigator or a person designated by the Investigator, must provide the subject enough time and opportunity to inquire about the details of the study and to decide whether or not to participate in the trial. All questions addressed by the subject about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2 ASSESSMENT OF ELIGIBILITY

The Investigator must assess subject' continued eligibility for the study as per the Inclusion and Exclusion criteria, during the Screening Period. The eligibility criteria are described in Section 3.3.1~~3.3.1~~ (Inclusion Criteria) and Section 3.3.2~~3.3.2~~ (Exclusion Criteria). In the event that the subject is not suitable or eligible for the study, the subject will be considered "screen failure".

7.2.1. Re-screening

If a subject fails initially to meet the eligibility criteria, and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once and may be enrolled in the study only if they meet all Inclusion and no Exclusion criteria when re-screened.

7.3 DEMOGRAPHIC INFORMATION AND BASELINE DISEASE CHARACTERISTICS

In this study the demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender

- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

In addition, the following baseline disease characteristics will be collected:

- Year of initial diagnosis,
- Tumor morphology (Ductal/NOS, Lobular, Medullary, Tubular, Other, or Unknown),
- Histologic grade (I, II, III, or Unknown),
- BRCA 1/2 status,
- Menstrual status,
- Location of metastasis (Brain, Visceral, Nonvisceral)

7.4 MEDICAL HISTORY

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.

Events that emerge prior to the first treatment (C1D1) will be recorded in the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to the subject's receiving investigational product treatment.

Medical histories will be recorded using the body system categories outlined below:

- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal
- Hepatic
- Neurological
- Endocrine
- Lymphatic
- Hematologic
- Immunologic
- Dermatologic
- Psychiatric
- Genitourinary
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition

- Date of diagnosis
- History status (resolved or ongoing).

7.5 CONCOMITANT MEDICATION

The subject may be applied any medications judged necessary by the Investigator, provided such medications are not listed in Section 7.5.2~~7.5.2~~.

All concomitant medication administered or taken by the subject beginning 30 days prior to Screening Visit and throughout the study will be recorded in the source documents and on the appropriate page of the Case Report Form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
- **Note:** Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing).

7.5.1. Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

7.5.2. Prohibited Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Period of this trial:

- Anti-cancer systemic chemotherapy or biological therapy other than Treatment of Physician's Choice (TPC)
- Investigational agents other than leronlimab (PRO 140)
- Radiation therapy

7.6 VITAL SIGNS, HEIGHT AND WEIGHT

The following will be collected:

- Vital signs:
    - Seated blood pressure (taken after the subject has been seated for at least 5 minutes)
    - Pulse
    - Temperature (oral or tympanic)
    - Respiratory Rate
- Height (at Screening Visit only) and Weight
- BMI (derived from the height and weight measurements).

7.7 PHYSICAL EXAMINATION

The physical examination will include routine examinations for the following:

- Head, Ears, Eyes, Nose, Throat (HEENT)
- Abnormalities of the extremities
- Neurologic abnormalities
- Heart/cardiovascular abnormalities
- Musculoskeletal abnormalities
- Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject; i.e., the abnormality is clinically significant.

Each abnormality will be recorded and the Investigator will record an assessment of its clinical significance.

7.8 ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status will be documented at screening, at T1 and every 3 weeks thereafter, and at End of Treatment (EOT) visit.

Table 7-1: ECOG Performance Status Scale

Grade	Description
0	Asymptomatic; Fully active, able to carry on all pre-disease performance without restriction
1	Symptomatic but completely ambulatory; Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Symptomatic, <50% in bed during the day; Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Symptomatic, >50% in bed, but not bedbound; Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Bedbound; Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

7.9 Electrocardiogram (ECG)

A resting supine 12-lead ECG will be conducted at the Screening Visit (SV), at baseline (C1D1), and at End of Treatment (EOT) visit. A 12-lead EKG will be repeated during the study only if clinically indicated and at the discretion of the treating physician. The results will be evaluated by the Investigator. The following parameters will be recorded: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the ECG reading as either normal or abnormal, and as either not clinically significant or clinically significant. If abnormalities are observed, each will be recorded.

7.10 TOXICITY ASSESSMENT

Any subject who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each subject will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table. Toxicity will be assessed according to CTCAE v 5.0 criteria. Also refer to Table 6-3~~Table 6-3~~ for the dose modification and management of leronlimab (PRO 140) for any toxicity.

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.

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.

7.11 CLINICAL LABORATORY ASSESSMENTS

Blood samples will be collected for analysis of the following parameters:

- Biochemistry and Complete Blood Count (CBC) Parameters: At Screening, T1 and every 3 weeks thereafter, and at the end of treatment (EOT).
- Serum pregnancy test (for female subjects of childbearing potential): At Screening
- Urine pregnancy test (for female subjects of childbearing potential): T1 and every 3 weeks thereafter
- CTCs PD-L1/CCR5 Analysis: T1 and every 3 weeks thereafter and at the end of treatment (EOT).
- CTC and CAMLs Analysis: T1 and every 3 weeks thereafter and at the end of treatment (EOT).

All laboratory reports will be reviewed by the Investigator. Abnormal results that are considered by the Investigator to be clinically significant, will be recorded as adverse events. If in the Investigator's judgment, in order to make the determination of clinical significance the testing may be needed to be repeated. Validated, quality-controlled laboratory data will be transferred to the main database for analyses.

Table 7-2: Central Lab Parameters

CBC Parameters	Biochemistry Parameters	Urinalysis
Hemoglobin	**Liver Function Tests**	pH
Hematocrit	Total Bilirubin	Appearance
RBC count	Direct Bilirubin	Color
WBC count	Alkaline Phosphatase (ALP)	Specific gravity
WBC Differential	Alanine Aminotransferase (ALT) (or SGPT)	Turbidity
Absolute lymphocyte count	Aspartate Aminotransferase (AST) (or SGOT)	Ketones
Absolute neutrophil count	Albumin	Bilirubin
Platelet count	Total Protein	Blood
Miscellaneous	**Renal Function Tests**	Glucose
Serum pregnancy test	Blood Urea Nitrogen (BUN)	Protein
Urine pregnancy test	Creatinine	Nitrites
(for female subjects of childbearing potential)	**Electrolytes**	Urobilinogen
Tissue for CCR5 expression (archival or fresh biopsy)	Sodium	Leukocyte esterases
Tissue for PD-L1 expression (archival or fresh biopsy)	Potassium	Microscopic exam includes bacteria, cast, crystals, epithelial cells, RBC and WBC.
CTCs PD-L1/CCR5	Chloride	
CTC CAMLs	Calcium	
	Bicarbonate	
	Other:	
	Glucose, Random, Serum	

7.11.1. Correlatives/Special Studies

Correlative Samples - Details for Lab Manual				
Correlative study (sample type)	**Tissue CCR5 Staining***	**Tissue PD-L1 Staining****	**CTC PD-L1/ CCR5**	**CTC, CAMLs**
Mandatory or Optional	Mandatory	Mandatory	Mandatory	Mandatory
Timing (+/- windows)	Archival or fresh	Archival or fresh	1-3 days	1-3 days
Volume Needed (blood only)	N/A	N/A	16 cc whole blood	20 cc whole blood for CTC and CAMLs
Tube type needed (blood only)	N/A	N/A	CellSave tube to be filled up completely.	CellSave tube to be filled up completely
Tissue thickness and/or # slides (tissue only)	5µ (No. of slides- TBD)	5µ (No. of slides- TBD)	N/A	N/A
Processing center (e.g. PCF- CTU)	PCF	TBD	CTCs Lab-NU	Creatv MicroTech, Inc

Correlative Samples - Details for Lab Manual				
Correlative study (sample type)	**Tissue CCR5 Staining***	**Tissue PD-L1 Staining****	**CTC PD-L1/ CCR5**	**CTC, CAMLs**
Sampling/ processing instructions	See lab manual	See lab manual	See lab manual	See lab manual
Shipping/delivery info	Medical College of Wisconsin (see below)	Reference laboratory	CTCs Lab-NU	Creatv MicroTech, Inc
Storage needs	Paraffin slides	Paraffin slides	See lab manual	See lab manual
Analysis center	See lab manual	See lab manual	CTC Lab-NU	See lab manual
Assay methodology	IHC	IHC	See below	See below

* 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 core or excisional biopsy to be done of the primary or metastatic site.

** 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.

7.11.1.1 Sample Collection Guidelines

Please refer to laboratory manual for more details

7.11.1.2 Sample Processing, Storage, and Shipment

For CCR5 and PD-L1 tissue analysis

FedEx shipping address:

[redacted]

For CTCs and CAML analysis

[redacted]

[redacted]

For CTC testing

[redacted]

7.11.1.3 Assay Methodology

CTCs Enumeration and PD-L1

CTC isolation and enumeration will be performed using the US Food and Drug Administration-approved CellSearch™ technology (Janssen Diagnostics). This technology consists of a semi-automated system for the preparation of a sample [Al-Kateb, 2015] and is used with the CellSearch™ Epithelial Cell Kit. The procedure enriches the sample for cells expressing the epithelial-cell adhesion molecule with antibody- coated magnetic beads, and labels the cells with the fluorescent nucleic acid dye 4,2-diamidino-2- phenylindole dihydrochloride (DAPI). Fluorescently labeled monoclonal antibodies specific for leukocytes (CD45-allophycocyan) and epithelial cells (cytokeratin 8, 18, 19-phycoerythrin) are used to distinguish epithelial cells from leukocytes. A PD-L1 expression kit has been developed and is currently tested in clinical trial evaluating PD-L1 or PD-1 therapeutic targeting antibodies.

CTCs and CAMLs using CellSieve™

The CellSieve™ microfiltration assay isolates circulating tumor cells (CTCs) and circulating cancer-associated macrophage-like cells (CAMLs) by size exclusion, identifying CTCs and CAMLs by their morphological features and the phenotypic expression of CCR5, cytokeratins 8, 18, and 19, CD45 and DAPI. Peripheral blood (7.5 mL) collected in CellSave preservative tubes is prefixed for 15 min, placed into the 30-mL syringe, and drawn through the filter in ~3 min. The filtration instrument utilizes negative pressure to draw the sample through the filters at a gentle continuous rate. The filter is then washed, postfixed, and permeabilized for 15 min. The filter and cells are stained with an antibody mixture and blocking buffer of FITC-conjugated anti-cytokeratin 8, 18, 19, phycoerythrin (PE)-conjugated CCR5, and Cyanine5-conjugated CD45 (Creatv MicroTech, Inc.).

CTCs are CD45 negative cells with a pleomorphic nucleus and a filamentous cytokeratin positive phenotype. CAMLs are large (21–300 µm in length) and morphologically distinct from CTCs. CAMLs are identified as single cells with an enlarged nuclear profile (14–64 µm in diameter) or separated polymorphic nuclei contained within the cell. In addition, the nuclei are surrounded by a larger CD45 signal. CAMLs can be identified further by vacuoles containing DAPI+ and/or cytokeratin.

7.12 STUDY TREATMENT APPLICATION

Refer to Section 6.16.1 for details.

7.13 POST-INJECTION EVALUATION AND INJECTION SITE REACTION ASSESSMENT

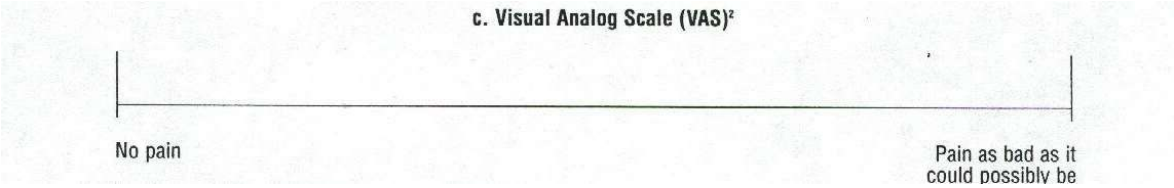
- At each treatment visit, an injection site reaction assessment will be made for the current and previous injection sites. Injection site reaction assessments are recorded by the Investigator starting after the first injection is given. Subject will be observed at approximately 30 minutes post-injection or longer if necessary for injection site reaction as per CTCAE v5.0. Refer to Sections 9.2.69.2.6 for more details.

7.14 PAIN ASSESSMENT USING VISUAL ANALOG SCALE (VAS)

Tolerability of repeated subcutaneous administration of leronlimab (PRO 140) is evaluated based on assessment of subject-perceived injection site pain using the Pain Visual Analog Scale (VAS). This assessment will be performed each time subjects arrive to the clinic for the study treatment visit.

Before and immediately after each study treatment administration, subjects will be asked to mark the point that best represents the pain intensity **over the past week** at the time of injection administration on a horizontal line (100 mm in length) anchored by the following word descriptors at each end, “no pain" on the left side and "pain as bad as it could possibly be" on the right side of the line. The subject marks on the line or by pointing to a position on the line the point that they feel represents their perception of their pain state. The VAS score is determined by measuring in millimeters from the left-hand end of the line to the point that the patient marks.

Figure 7-1: Visual Analog Scale



7.15 TUMOR IMAGING AND RESPONSE EVALUATION

For the purposes of this study, patients should be re-evaluated for tumor response approximately every 3 months or according to institution’s standard practice. In addition to a baseline scan,

confirmatory scans should also be obtained 4-8 weeks following initial documentation of objective response greater than Stable Disease (SD).

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

High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of registration. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in all eligible subjects. All known or suspected sites of disease (including CNS if history of CNS metastases) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST v1.1 should be used when recording data, and should again be used for all subsequent assessments. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Radiographic tumor assessments will be conducted approximately every 3 months or according to institution's standard practice by CT or MRI (per treating investigator's discretion); the same modality used at baseline should be used throughout. Tumor measurements will be done using RECIST v1.1. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST.

7.15.1. Definition of Lesions

Tumor response will be assessed according to the RECIST (version 1.1; *Eisenhauer et al*. 2009). At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with

CT scan, MRI, or calipers by clinical exam (such measurements must be clearly documented). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes:

To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions.

Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if

noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

7.15.2. Method of Assessment

The same method of assessment and the same technique have to be used to characterize each identified and reported lesion at screening, at end of treatment and during follow-up.

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes).

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

Conventional CT and MRI should be performed with contiguous cuts of 5 mm or less in slice thickness, if possible [minimum measurable lesion size: long axis ≥ 10 mm (CT + MRI) and 2 x slice thickness, if the slice thickness is > 5 mm].

Ultrasound may only be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules.

7.15.3. Baseline documentation of 'target' and 'non-target' lesions

Only subjects with measurable disease at baseline should be enrolled in this study. For evaluation of tumor response, lesions present at screening will be separated into target and non-target lesions according to the following criteria:

Target Lesions:

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

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

Non-Target Lesions

- All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

7.15.4. Evaluation of target lesions

- Measure LD (axial plane) for each target lesion
- Measure short axis for target lymph nodes
- Add these measurements to get the SLD
- If too small to measure, a default value of 5 mm is assigned. If the lesion disappears completely, the measurement is recorded as 0 mm.
- Splitting or coalescent lesions
- If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum
- If target lesions coalesce, the LD of the resulting coalescent lesion is added to the sum

Table 7-3: Target Lesion Evaluation

• Response	• Definition
• Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
• Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum

• Response	• Definition
	diameters.
• Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
• Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.15.5. Evaluation of non-target lesions

Table 7-4: Non-Target Lesion Evaluation

• Response	• Definition
• Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
• Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
• Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

7.15.6. Evaluation of Best Overall Response

The best overall response is the best response recorded from start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Responses will be assessed using CT scans or magnetic resonance imaging according to standard RECIST v1.1 criteria in order to assess disease progression. These criteria will also allow for patients who experience an initial disease flare, and as some patients who will have a delayed response may experience an initial disease flare, these patients will be allowed to continue receiving study treatment beyond progression.

The following table provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions:

Table 7-5: Time point response: subjects with target (± non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Note: To be assigned a status of PR or CR, changes in tumor measurements must be

Target lesions	Non-target lesions	New lesions	Overall response

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.

7.15.7. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met category when no lesions can be measured is not advised for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

7.16 SURVIVAL STATUS

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.

7.17 TREATMENT OF PHYSICIAN'S CHOICE

Treatment of Physician's Choice (TPC) is defined as the following drugs administrated according to local practice:

- Eribulin
- Gemcitabine
- Capecitabine
- Paclitaxel
- Nab-paclitaxel
- Carboplatin
- Atezolizumab (or other checkpoint inhibitors)

The selected treatment should be administered as per the dosing schedule included on the package insert.

8 STATISTICAL ANALYSIS

This section presents general information about statistical considerations and concepts and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

8.1 TREATMENT GROUPS

- 525 mg leronlimab (PRO 140)

8.2 SAMPLE SIZE DETERMINATION AND RATIONALE

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.

8.3 RANDOMIZATION AND STRATIFICATION

Not applicable.

8.4 BLINDING

Not applicable.

8.5 INTERIM ANALYSIS

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

8.6 STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.3 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

8.6.1. Analysis Populations

8.6.1.1 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

8.6.1.2 Per Protocol 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

8.6.1.3 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.

8.6.2. Covariates

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.

8.6.3. Missing Data

All data will be used as observed, and no imputations will be made for any missing data point for early phase study.

8.7 ANALYSIS METHODS

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the data from this trial.

8.7.1. Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, enrolled, completed, and discontinued during the study, as well as the reasons for all post-enrollment discontinuations will be listed and/or summarized by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

8.7.2. Demographic and Baseline Disease Characteristics

Demographics and baseline disease characteristics including medical history, prior and concomitant medications/therapies will be listed and/or summarized by treatment group using appropriate descriptive statistics.

8.7.3. Study Analyses

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+ 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

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.

- 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.

Exploratory Outcome (Endpoints) 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.

PFS will be calculated using Kaplan-Meier curves and the median PFS will be read from this curve. Response rates (overall response rate, clinical benefit rate) will be calculated using proportions and 95% confidence intervals. Time to new metastases and overall survival will also be analyzed using Kaplan-Meier curves. Exploratory serial blood markers will be related to PFS using Cox regression, and to response using logistic regression.

8.7.3.1 Safety Analyses

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 at each visit for potential AEs and disease related signs and symptoms. The CTCAE v5.0 will be used to grade toxicities / AEs.

The Safety population will be used for the analysis of safety endpoints.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical variables.

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:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade (mild, moderate, severe, or life threatening for SAEs)
- By relationship to clinical trial treatment according to the mapping scheme below:
  - Potentially related: will include all adverse events with a relationship rating of "definitely", "probably" or "possibly".
  - Unlikely/not related: will include all adverse events with a relationship rating of "unlikely" or "unrelated".

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized as continuous variable and presented by treatment group and time point.

Physical Examination

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

Vital Signs

All vital sign findings will be listed and summarized.

Electrocardiograms (ECGs)

All ECG findings will be listed and summarized.

Eastern Cooperative Oncology Group (ECOG) performance status

All ECOG performance status findings will be listed and summarized.

9 ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this Section of the protocol.

9.1 ADVERSE EVENT (AE)

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the subject to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormalities in visit evaluations, physical examination findings or laboratory results that the investigator believes are clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should be not be recorded as an AE

9.2 REPORTING AND FOLLOW-UP OF ADVERSE EVENTS

Report initiation for all AEs and serious adverse events (SAEs), (see Section 9.3~~9.3~~), will begin at the time of the first treatment and continue up to the final study visit. All events will be followed to resolution or until 30 days after the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be a SAE (see Section 9.3~~9.3~~), the impact the event had on study treatment (see Section 9.2.1~~9.2.1~~), the CTCAE grade (intensity) of the event (see Section 9.2.2~~9.2.2~~), the causality of the event (see Section 9.2.3~~9.2.3~~), whether treatment was given as a result of the event (see Section 9.2.4), and the outcome of the event (see Section 9.2.5~~9.2.5~~).

9.2.1. Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the subject is no longer in the treatment period of the protocol or died.

9.2.2. CTCAE Grade (Intensity) Assessment

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Table 9-1: CTCAE v5.0 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.‡

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
‡Unlike the AE outcome assessment (see Section 9.2.5~~9.2.5~~), a subject may have more than one Grade 5 event.

-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: Nov 27, 2017

9.2.3. Causality Assessment

Adverse events will be assigned a relationship (causality) to the study treatment or TPC (standard of care chemotherapy or immunotherapy). The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Unrelated** – The event is definitely not associated with the study biologic or control. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication explain the reported AE.
2. **Unlikely** – The temporal association, patient history and/or circumstances are such that the study biologic or control is not likely to have had an association with the observed event. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication, appear to explain the reported AE.
3. **Possibly** – The event follows a reasonable temporal sequence from study biologic or control but could have been produced by the patient's clinical state or other therapies administered to the patient.
4. **Probably** – The event follows a reasonable temporal sequence from the study biologic or control, abates upon discontinuation of the study drug or control, or cannot be reasonably explained by known characteristics of the patient's clinical state.

5. **Definitely** – The event follows a reasonable temporal sequence from the study biologic or control, abates upon discontinuation and cannot be explained by known characteristics of the patient's clinical state.

9.2.4. Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

9.2.5. Outcome Assessment

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

9.2.6. Injection-site reactions

Injection-site reactions thought to be directly related to the injection are considered to be AEs of special interest, and will be assessed as per CTCAE v5.0.

For subjects who develop Grade 1 or Grade 2 events, therapy will be continued as per protocol. If a subject chooses to discontinue study treatment, the site should notify the protocol team leadership, and encourage the subject to complete any remaining study visits until the toxicity resolves.

For subjects who develop Grade 3 events following study drug injection, the subject should be reevaluated closely until the AE returns to Grade 1 or less, at which time study treatment may be reintroduced at the discretion of the site investigator. If the same Grade 3 AE recurs following the next administration of study drug, study treatment must be permanently discontinued. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed closely for resolution of the AE to Grade 1 or less and the team leadership must be notified.

For Grade 4 events permanently discontinue therapy.

9.3 SERIOUS ADVERSE EVENTS

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the adverse experience)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

9.4 REPORTING OF SERIOUS ADVERSE EVENTS

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.2~~9.2~~. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Amarex Safety and Pharmacovigilance Department within 24 hours:

CRO Medical Monitor	[redacted]

A written SAE reports must include a full description of the event as described in Section 9.2~~9.2~~ and must follow within 24 hours from the time the Investigator first learned of the event. The Amarex Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram [ECG] reports, discharge summary, hospital notes, etc, if applicable.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

9.5 SAE FOLLOW-UP

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA, the monitors, auditors and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 MONITORING REQUIREMENTS

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

As delineated above, the Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but are not limited to study, laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated and stated the type of visit. The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

11.2 ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

For each subject who has signed an informed consent form, a CRF must be completed. For subjects who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed as soon as possible after the subject's visit and corrections to data on the CRFs will be documented, if applicable. The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

11.3 MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator's IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be provided in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4 REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

11.4.1. Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior sponsor and IRB approval.

- Multiple minor violations of the same nature after multiple warnings.

11.4.2. Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow-up visits that occurred outside the protocol required time frame because of the participant’s schedule.
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

12 DATA SAFETY MONITORING BOARD (DSMB)

The study will be monitored by an independent DSMB to ensure patient safety. The CRO is responsible for the overall management of DSMB, including development of its charter and membership selection. The DSMB will be managed in conformance with the FDA guidelines for DSMB independence, management, and oversight.

The DSMB will consist of at least three members and will review unexpected AEs, related AEs, SAEs, and deaths, according to the study's phase and risk level, as outlined in the DSMB charter.

All expedited safety reports will be provided in real time to the DSMB chair upon being reported to FDA.

Note: For the purpose of expedited safety reporting, all adverse events except skin reactions will be considered unexpected.

The DSMB will make the following recommendations at each safety evaluation:

- Continue the study as planned;
- Assess a specific aspect of safety that is not conclusive;
- Gather more data to address a specific safety issue; and
- Stop the study due to safety concerns.

Additionally, DSMB may recommend protocol modifications or other actions including but not limited to the following:

- Discontinuing or modifying a study based on safety information obtained from the protocol or from information external to the trial
- Changing the eligibility criteria if the risks of the intervention appear to be higher in a particular subset of patients
- Altering the drug dosage and/or schedule if the adverse events observed appear likely to be mitigated by such changes
- Instituting screening procedures that could identify those subjects at increased risk of a particular adverse event
- Identifying information needed to inform current and future trial subjects of newly identified risks via changes in the informed consent document and, if appropriate, recommending re-consent of current subjects to continue trial participation.

The Sponsor retains the responsibility to contact FDA and the final decision regarding the

recommendation to continue or to terminate the study.

13 ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

13.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator (PI) at the site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

13.2 INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated

Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding to the study center participating in this study that cannot comply with these standards will be documented.

13.3 SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the subject. Written informed consent will be obtained from each subject prior any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form ICF will be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject's medical record, if allowed by institutional policy.

14 DATA HANDLING AND RECORD KEEPING

14.1 RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve case report forms (CRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

14.2 CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

14.3 ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- IP and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening
- SAE reports
- IRB approval and re-approval letters
- Completed quality of life questionnaire
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

15 PUBLICATION PLAN

All information supplied by CytoDyn in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of CytoDyn, shall not be disclosed to others without the written consent of CytoDyn, and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of CytoDyn. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: The site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the multi-center trial or the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

16 REFERENCES

Adams DL, Martin SS, Alpaugh RK, Charpentier M, Tsai S, Bergan RC, Ogden IM, Catalona W, Chumsri S, Tang CM, Cristofanilli M. Circulating giant macrophages as a potential biomarker of solid tumors. PNAS 2014;111:3514–3519.

Adams DL, Adams DK, He J, Kalhor N, Zhang M, Xu T, Gao H, Reuben JM, Qiao Y, Komaki R, Liao Z, Edelman MJ, Tang C-M, Lin SH, Sequential tracking of PD-L1 expression and RAD50 induction in circulating tumor and stromal cells of lung cancer patients undergoing radiotherapy, Clinical Cancer Research, 2017; 23:5948-5959.

Adams DL, Adams DK, Lin SH, Cristofanilli M, Bergan RC, Marks J, Martin SS, Chumsri S, Ho TH, Lapidus RG, Tsai S, Tang CM, Katherine Alpaugh RK, Cancer-associated macrophage-like cells as prognostic indicators of overall survival in a variety of solid malignancies. Power Point presentation on ASCO website. https://meetinglibrary.asco.org/results/adams%20caml;page=1

Al-Kateb H, Nguyen TT, Steger-May K, Pfeifer JD. Identification of major factors associated with failed clinical molecular oncology testing performed by next generation sequencing (NGS). Molecular oncology. 2015 Nov 1;9(9):1737-43.

Bidard FC, Peeters DJ, Fehm T, Nolé F, Gisbert-Criado R, Mavroudis D, Grisanti S, Generali D, Garcia-Saenz JA, Stebbing J, Caldas C. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. The Lancet Oncology. 2014 Apr 1;15(4):406-14.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. New England Journal of Medicine. 2015 Oct 22;373(17):1627-39.

Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. New England Journal of Medicine. 2015 Jul 9;373(2):123-35.

Chow MT, Luster AD. Chemokines in cancer. Cancer immunology research 2 (12): 1125–1131. doi: 10.1158/2326-6066. CIR-14-0160.[PMC free article][Abstract][Cross Ref]; 2014.

Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, Reuben JM, Doyle GV, Allard WJ, Terstappen LW, Hayes DF. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. New England Journal of Medicine. 2004 Aug 19;351(8):781-91.

Dawood S, Hu R, Homes MD, Collins LC, Schnitt SJ, Connolly J, Colditz GA, Tamimi RM. Defining breast cancer prognosis based on molecular phenotypes: results from a large cohort study. Breast cancer research and treatment. 2011 Feb 1;126(1):185-92.

de Oliveira CE, Gasparoto TH, Pinheiro CR, Amôr NG, Nogueira MR, Kaneno R, Garlet GP, Lara VS, Silva JS, Cavassani KA, Campanelli AP. CCR5-dependent homing of T regulatory cells to the tumor microenvironment contributes to skin squamous cell carcinoma development. Molecular cancer therapeutics. 2017 Dec 1;16(12):2871-80.

Del Prete A, Schioppa T, Tiberio L, Stabile H, Sozzani S. Leukocyte trafficking in tumor microenvironment. Current opinion in pharmacology. 2017 Aug 1;35:40-7.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009 Jan 1;45(2):228-47.

Engstrøm MJ, Opdahl S, Hagen AI, Romundstad PR, Akslen LA, Haugen OA, Vatten LJ, Bofin AM. Molecular subtypes, histopathological grade and survival in a historic cohort of breast cancer patients. Breast cancer research and treatment. 2013 Aug 1;140(3):463-73.

Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. New England journal of medicine. 2010 Nov 11;363(20):1938-48.

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E. Pembrolizumab for the treatment of non–small-cell lung cancer. New England Journal of Medicine. 2015 May 21;372(21):2018-28.

Halama N, Zoernig I, Berthel A, Kahlert C, Klupp F, Suarez-Carmona M, Suetterlin T, Brand K, Krauss J, Lasitschka F, Lerchl T. Tumoral immune cell exploitation in colorectal cancer metastases can be targeted effectively by anti-CCR5 therapy in cancer patients. Cancer cell. 2016 Apr 11;29(4):587-601.

Harbeck, N., & Gnant, M. (2016). Breast cancer. The Lancet, 389(10074), 1134–1150. https://doi.org/10.1016/S0140-6736(16)31891-8

Jacobson JM, Saag MS, Thompson MA, Fischl MA, Liporace R, Reichman RC, Redfield RR, Fichtenbaum CJ, Zingman BS, Patel MC, Murga JD. Antiviral activity of single-dose PRO 140, a CCR5 monoclonal antibody, in HIV-infected adults. Journal of Infectious Diseases. 2008 Nov 1;198(9):1345-52.

Jacobson JM, Lalezari JP, Thompson MA, Fichtenbaum CJ, Saag MS, Zingman BS, D'Ambrosio P, Stambler N, Rotshteyn Y, Marozsan AJ, Maddon PJ. Phase 2a study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. Antimicrobial agents and chemotherapy. 2010 Oct 1;54(10):4137-42.

Lanitis E, Dangaj D, Irving M, Coukos G. Mechanisms regulating T-cell infiltration and activity in solid tumors. Annals of Oncology. 2017 Sep 21;28(suppl_12):xii18-32.

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. New England Journal of Medicine. 2015 Jul 2;373(1):23-34.

Luboshits G, Shina S, Kaplan O, Engelberg S, Nass D, Lifshitz-Mercer B, Chaitchik S, Keydar I, Ben-Baruch A. Elevated expression of the CC chemokine regulated on activation, normal T cell expressed and secreted (RANTES) in advanced breast carcinoma. Cancer research. 1999 Sep 15;59(18):4681-7.

Malorni L, Shetty PB, De Angelis C, Hilsenbeck S, Rimawi MF, Elledge R, Osborne CK, De Placido S, Arpino G. Clinical and biologic features of triple-negative breast cancers in a large cohort of patients with long-term follow-up. Breast cancer research and treatment. 2012 Dec 1;136(3):795-804.

Mañes S, Mira E, Colomer R, Montero S, Real LM, Gómez-Moutón C, Jiménez-Baranda S, Garzón A, Lacalle RA, Harshman K, Ruíz A. CCR5 expression influences the progression of human breast cancer in a p53-dependent manner. Journal of Experimental Medicine. 2003 Nov 3;198(9):1381-9.

Moser B, Loetscher P. Lymphocyte traffic control by chemokines. Nature immunology. 2001 Feb;2(2):123.

Neagu M, Constantin C, Longo C. Chemokines in the melanoma metastasis biomarkers portrait. Journal of Immunoassay and Immunochemistry. 2015 Nov 2;36(6):559-66.

Niwa Y, Akamatsu H, Niwa H, Sumi H, Ozaki Y, Abe A. Correlation of tissue and plasma RANTES levels with disease course in patients with breast or cervical cancer. Clinical cancer research. 2001 Feb 1;7(2):285-9.

Paget S. The distribution of secondary growths in cancer of the breast. The Lancet. 1889 Mar 23;133(3421):571-3.

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J. Pembrolizumab versus ipilimumab in advanced melanoma. New England Journal of Medicine. 2015 Jun 25;372(26):2521-32.

Thompson M, Lalezari J, Saag M, Jacobson J, Zingman B, Stambler N, D'Ambrosio P, Maddon P, Olson W, Morris S. Weekly and biweekly subcutaneous PRO 140 demonstrates potent, sustained antiviral activity. In16th Conference on Retroviruses and Opportunistic Infections 2009 Feb 8 (pp. 8-11).

US Food and Drug Administration. The establishment and operation of clinical trial data monitoring committees for clinical trial sponsors. https://www.fda.gov/downloads/regulatory information/guidances/ucm127073.pdf.

Velasco-Velázquez M, Jiao X, De La Fuente M, Pestell TG, Ertel A, Lisanti MP, Pestell RG. CCR5 antagonist blocks metastasis of basal breast cancer cells. Cancer research. 2012 May 25:canres-3917.

Walens A, DiMarco AV, Lupo R, Kroger BR, Damrauer JS, Alvarez JV. CCL5 promotes breast cancer recurrence through macrophage recruitment in residual tumors. eLife. 2019 Apr 16;8:e43653.

Zhang Y, Yao F, Yao X, Yi C, Tan C, Wei L, Sun S. Role of CCL5 in invasion, proliferation and proportion of CD44+/CD24− phenotype of MCF-7 cells and correlation of CCL5 and CCR5 expression with breast cancer progression. Oncology reports. 2009 Apr 1;21(4):1113-21.

17 APPENDIX

17.1 APPENDIX 1: ACCEPTABLE METHODS OF CONTRACEPTION

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Male condom plus spermicide • Cap plus spermicide • Diaphragm plus spermicide	• Copper T • Progesterone T • Levonorgestrel-releasing	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

NOTE: choice of contraception should be discussed with primary treating oncologist to discuss the risks and benefits of different modalities of contraception.

17.2 APPENDIX 2: RECOMMENDATIONS FOR HER-2 TESTING IN BREAST CANCER

Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.

Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF; American Society of Clinical Oncology; College of American Pathologists.

J Clin Oncol. 2013 Nov 1;31(31):3997-4013. doi: 10.1200/JCO.2013.50.9984. Epub 2013 Oct 7.

For complete detailed information please refer to the link below:

http://ascopubs.org/doi/full/10.1200/JCO.2013.50.9984

17.3 APPENDIX 3: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0

For complete detailed information please refer to the link below:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf