CLINICAL STUDY PROTOCOL

PHASE 1/2a STUDY OF DOUBLE-IMMUNE SUPPRESSION BLOCKADE BY COMBINING A CSF1R INHIBITOR (PLX3397) WITH AN ANTI-PD-1 ANTIBODY (PEMBROLIZUMAB) TO TREAT ADVANCED MELANOMA AND OTHER SOLID TUMORS

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INVESTIGATOR AGREEMENT

PHASE 1/2a STUDY OF DOUBLE-IMMUNE SUPPRESSION BLOCKADE BY COMBINING A CSF1R INHIBITOR (PLX3397) WITH AN ANTI-PD-1 ANTIBODY (PEMBROLIZUMAB) TO TREAT ADVANCED MELANOMA AND OTHER SOLID TUMORS

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Plexxikon representative listed below.

[redacted]	[redacted]
Print Name	**Signature**
Chief Medical Officer	15 Dec 2017
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

IND Number:	105,521
Protocol Number:	PLX108-14
Investigational Product:	PLX3397 in combination with pembrolizumab
Active Ingredient(s)/ International Non-proprietary Name:	PLX3397: CSF1R inhibitor Pembrolizumab: Humanized monoclonal antibody (mAb) that blocks the programmed cell death (PD-1) receptor
Study Title:	Phase 1/2a Study of Double-Immune Suppression Blockade by Combining a CSF1R Inhibitor (PLX3397) with an Anti-PD-1 Antibody (Pembrolizumab) to Treat Advanced Melanoma and Other Solid Tumors
Study Phase:	Phase 1/2a
Indication Under Investigation:	**Dose-escalation Phase:** Advanced solid tumors, all comers **Expansion Phase:** The following tumor types: • Melanoma (treatment-naïve) • Melanoma (primary progressive) • Melanoma (secondary progressive) • Non-small-cell lung cancer (NSCLC; non-squamous; EGFR, ALK wild type) • Ovarian cancer • Triple-negative breast cancer (TNBC) • Squamous cell cancer of the head and neck • Clear cell renal cell carcinoma (CCRCC) • Pancreatic ductal adenocarcinoma • Gastric cancer • Glioblastoma multiforme (GBM) • Gastrointestinal stromal tumor (GIST) • High grade soft tissue sarcoma • Cholangiocarcinoma

Study Objectives:	**Primary Objectives** • To establish the recommended phase 2 dose (RP2D) and schedule of PLX3397 for the combination of PLX3397 and pembrolizumab. • To determine the safety and tolerability of combination of the CSF-1R inhibitor PLX3397 and the anti-PD-1 antibody pembrolizumab. **Secondary Objectives** • To define the adverse event (AE) profile of the combination of PLX3397 and pembrolizumab and to determine the relationship of AEs to study treatment. • To evaluate objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECISTv1.1) guidelines, relative to the assumed historical control rate for pembrolizumab, for each of the tumor types in subjects treated with the RP2D of PLX3397 for the combination of PLX3397 and pembrolizumab (Expansion Phase). Subjects with each of the tumor types will also by analyzed by RECISTv1.1 for progression-free survival (PFS). **Exploratory Objectives for Dose-escalation and Expansion Phases** • To evaluate biomarkers of drug effects on liver. • To evaluate biomarkers of treatment effects, including but not limited to myeloid-derived suppressor cell (MDSC) function. • To evaluate ORR by immune-related RECIST (irRECIST) guidelines, relative to the assumed historical control rate for pembrolizumab in subjects treated with the RP2D for the combination of PLX3397 and pembrolizumab (Expansion Phase). • To determine effects of the combination of PLX3397 and pembrolizumab on multiple biomarkers of disease or treatment, through analysis of available paired tumor biopsy samples using methods that include but are not limited to Nanostring and IHC of intratumoral CD68+ macrophages and CD8+ T-cells. Optional baseline and 28-day post-treatment biopsies will be collected in the Dose-escalation phase and will be

	mandatory in the Expansion Phase, unless deemed medically unsafe by the Investigator.
Study Design:	Phase 1/2a, 2-part, open-label clinical study comprised of a Dose-escalation Phase followed by an Expansion Phase. **Dose-escalation Phase:** Up to 42 subjects with advanced solid tumors (any type) will be enrolled sequentially in up to 7 cohorts of 3 to 6 subjects using a standard 3+3 design. Subjects will receive pembrolizumab 200 mg IV every 3 weeks in combination with a starting dose of PLX3397 at 600 mg/day (administered twice daily as a split dose of 200 mg in the morning and 400 mg in the evening), with sequential escalations to 800 and 1000 mg/day. (If the 600 mg/day dose of PLX3397 is not well tolerated, de-escalation to 400 mg/day will be allowed). The goal of this phase is to determine the RP2D of PLX3397 in combination with a fixed dose of pembrolizumab, defined as the maximum tolerated dose (MTD) or maximum administered dose of PLX3397. The MTD is defined as the dose level below the one at which more than 1 of 6 subjects experience DLT in Cycle 1 during the 42-day DLT window. If the MTD cannot be determined because of a lack of a DLT during the 42-day DLT window, the MAD of PLX3397 will be declared the RP2D. The MAD is defined as the maximum dose proposed to be administered during the study, i.e., PLX3397 administered orally at 1000 mg/day (as a split dose) in combination with pembrolizumab. The RP2D will be confirmed with at least 6 subjects. Subjects who complete the Dose-escalation Phase may continue in the study and receive treatment at the dose assigned to their cohort, assuming that dose is considered pharmacodynamically active, or these subjects can be titrated up to the RP2D at the discretion of the Investigator. The recommended phase 2 dose (RP2D) of PLX3397 in combination with pembrolizumab 200 mg every 3 weeks is 600 mg/day (as a split dose, 200 mg in the morning and 400 mg in the evening) based on the incidence observed toxicities (i.e., ≥2 patients with DLT at a higher dose level) and overall tolerability. **Expansion Phase:** The design of the expansion phase uses a truncated sequential probability ratio test for single-arm binary response studies. Subjects with advanced solid tumors of any 1 of the tumor types will receive pembrolizumab 200 mg IV every 3 weeks in combination with the RP2D of PLX3397. Dosing will continue until a subject experiences disease progression as determined by irRECIST, unacceptable

	toxicity, or meets any other discontinuation criterion such as meeting criteria for a complete response **Dose Decrements:** Throughout the study, dose decrements of 200 mg/day of PLX3397 are permitted for management of toxicity.
Study Duration:	~12 months to complete the Dose-escalation Phase and up to 2 years to enroll subjects in and subsequently complete the Expansion Phase.
Study Sites and Location:	The Dose-escalation Phase will be conducted at up to 5 study sites in the US. Additional sites may be added for the Expansion Phase.
Planned Sample Size:	• **Dose-escalation Phase:** Up to 42 subjects in up to 7 cohorts, each a different dose or regimen. The number of subjects is not based on statistical power considerations. Three to 6 subjects will be accrued per dose level or regimen in order to insure the safety and tolerability. • **Expansion Phase:** Up to 483 subjects, with the sample size for each of the tumor types based on a truncated sequential probability ratio test. The maximum sample size will be 28 to 48 subjects per tumor type, depending on the null response within each tumor type.
Subject Eligibility — Inclusion Criteria:	A subject must satisfy all of the following criteria to be considered for inclusion in the study: 1. Be willing and able to provide written informed consent for the trial. 2. Male or female ≥18 years old. 3. Subjects with histologically or cytologically-confirmed diagnosis of cancer that is recurrent, metastatic, or persistent, who have relapsed from or are refractory to treatment, and who also meet the following corresponding requirements for the cohort or phase of the study they into which they will enroll: • **Dose-escalation Phase:** Subjects with advanced solid tumors (any tumor type) considered to have no standard-of-care treatment for their malignancy with a curative intent, either as initial therapy or after progressing to prior therapies; subjects who have been treated previously with a CSF1R inhibitor or an anti-PD1/PDL1 inhibitor

may enroll.

- **Expansion Phase:** Subjects with 1 of the tumor types who have relapsed from or are refractory to standard treatment. Subjects with:

  i. NSCLC (non-squamous; EGFR and ALK wild-type) and SCCHN cancer must show primary progression (i.e., no partial or complete response [PR or CR]) with anti-PD1/anti-PDL1 therapy

  ii. Melanoma subgroups are as follows: (a) anti-PD-1 /PD-L1 naïve and CSF1R naïve; (b) at least 4 months of prior anti-PD-1 PD-L1 therapy but never responded (i.e., no PR or CR); (c) prior anti-PD-1 /PD-L1 therapy and responded but later progressed as defined by irRECIST while on therapy

  iii. Ovarian includes primary peritoneal and fallopian tube cancers; (carcinosarcomas and low grade serous tumors are excluded)

  iv. Unresectable RCC with component of clear-cell histology and/or component of sarcomatoid histology

  v. World Health Organization Grade IV supratentorial malignant glioma (glioblastoma or gliosarcoma) following complete or partial surgical resection and radiation plus temozolomide

  vi. Gastrointestinal stromal tumor (GIST) cohort must have locally advanced or metastatic disease and have progressed on or have been intolerant to imatinib therapy

  vii. All tumor types must be naïve to anti-PD1/PDL1 inhibitors except as described in (i) and (ii).

4. Subjects with melanoma must have a histologically confirmed diagnosis of stage III or stage IV disease not amenable to local therapy. Melanoma subjects may have received any number of prior lines of therapy for metastatic disease and must have measurable disease per RECISTv1.1. Cutaneous lesions and other superficial lesions that are detectable only by physical examination are not

	considered measurable lesions for the purposes of this protocol, but may be considered as non-target lesions. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Subjects with melanoma who have received prior treatment with a MEK/BRAF inhibitor are acceptable candidates. 5. **Expansion cohorts:** Subjects must have relapsed or been refractory to standard treatment and have measurable disease per RECISTv1.1, using computed tomography (CT) or magnetic resonance imaging (MRI), with [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography-computer tomography (PET/CT) for GIST subjects only. They must have tumor accessible for sequential biopsy (core needle biopsy or excision required) and be willing to provide on-study tumor tissue biopsy. When possible, newly obtained tissue should be collected from a non-target lesion. Repeat samples may be required if adequate tissue is not provided. Subjects for whom newly obtained samples cannot be obtained (e.g., inaccessible or patient safety concern; glioblastoma tumor type) may submit an archived specimen only upon agreement from the Sponsor. 6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. 7. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to initiation of dosing. 8. Women of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Effective forms of contraception include abstinence, hormonal contraceptive in conjunction with a barrier method, or a double-barrier method. Women of non-child bearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. 9. Fertile men must agree to use an effective method of birth control starting with the first dose of study treatment through 120 days after the last dose of study treatment.

10. Adequate organ function as demonstrated by the laboratory values shown below. These laboratory tests should be performed within 10 days of the first dose of study treatment.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine OR Measured or calculated[a] creatinine clearance (crcl) (GFR can also be used in place of creatinine or crcl)	≤1.5 × ULN OR ≥60 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.25 × ULN (Gilbert's syndrome allowed)
AST and ALT	≤1.5 × ULN
Coagulation	
International normalized ratio or prothrombin time (PT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

aPTT = activated partial thromboplastin time; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; INR = International Normalized Ratio; PT = Prothrombin time; ULN = upper limit of normal

[a] Creatinine clearance should be calculated per institutional standard.

Subject Eligibility — Exclusion Criteria:

A subject who meets any of the following criteria will be disqualified from entering the study:

1. Disease that is suitable for local therapy administered with curative intent.
2. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
3. 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 the first dose of study treatment. 4. Has had monoclonal antibody treatment for cancer within 28 days of first dose of study treatment or has not recovered from AEs due to agents administered more than 28 days earlier (i.e., AEs should be ≤Grade 1 or ≤the value collected at baseline). 5. Has had chemotherapy, targeted small molecule therapy, or radiation therapy >30 Gray within 14 days prior to first dose of study treatment or who has not recovered (i.e., AEs should be ≤Grade 1 or ≤the value collected at baseline) from AEs due to a previously administered intervention Note: Subjects with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study. 6. Has received transfusion of blood products (including platelets or red blood cells [RBC]) or administration of colony stimulating factors (including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or recombinant erythropoietin) within 28 days prior Day 1. 7. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. 8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer and isolated elevation of prostate-specific antigen. Subjects with a completely treated prior malignancy with no evidence of disease for ≥2 years are eligible. 9. Dose-escalation Cohort [-1]: Patients with liver metastases; inclusion of patients with liver metastases in subsequent cohorts will be based upon clinical safety data. 10. For Expansion cohort subjects who have previously received an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or has previously participated in pembrolizumab clinical trials are excluded, except those tumor types listed under Inclusion Criteria #3. 11. Has active autoimmune disease that has required

	systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. 12. Has an active infection requiring systemic therapy. 13. Has known central nervous system metastases and/or carcinomatous meningitis. Note: Subjects with previously treated brain metastases may participate if they meet the following criteria: 1) are stable (i.e., no evidence of progression per irRECIST [see the irRECIST Tip Sheet, provided in the Study Reference Manual] determined by imaging, using the identical imaging modality for each assessment, either MRI or CT scan) for at least 35 days prior to the first dose of study treatment and if all neurologic symptoms returned to baseline, 2) have no evidence of new or enlarging brain metastases, and 3) have not been using steroids for at least 7 days prior to first dose of study treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability. 14. Uncontrolled intercurrent illness. 15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate absorption. 16. QT interval corrected using Fridericia's formula (QTc) ≥450 msec (males) or ≥470 msec (females) at Screening. 17. Congenital long QT syndrome or patients taking concomitant medications known to prolong the QT interval. A list of drugs known to prolong the QT interval can be found in Appendix 17.1. 18. Major surgery within 28 days prior to first dose of study treatment. Note: If subject received major surgery, he or she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment. 19. History of active ethanol abuse.

	20. Has received a live vaccine administered within 30 days of planned treatment start or while participating in the trial. Seasonal flu vaccines that do not contain live virus are permitted. 21. 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. 22. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). 23. Any of the following within 48 weeks (~1 year) prior to first dose of study treatment: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack. 24. Imprisoned or under legal guardianship. 25. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment. 26. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 27. Has had prior exposure to PLX3397. 28. Has had hypersensitivity (≥Grade 3) reaction to pembrolizumab and/or any of its excipients.
Dosage Form, Dose and Route of Administration:	**Dose-escalation Phase:** Subjects receive pembrolizumab 200 mg IV every 3 weeks in combination with a starting dose of PLX3397 at 600 mg/day, with sequential escalations to 800 and 1000 mg/day. (If the 600 mg/day dose of PLX3397 is not well tolerated, de-escalation to 400 mg/day will be allowed.) If 400 mg/day is tolerated (i.e., no DLTs in 3 subjects or ≤1 DLT in 6 subjects), then re-escalation to 600 mg/day may be considered within the hepatic laboratory test limits in inclusion #10. Further dose escalation will be considered depending upon safety and tolerability of each cohort. PLX3397 is administered orally twice daily as a split

	dose. An intermediate dose level may be studied and may comprise alternative dosing regimens such as intermittent dosing (e.g., 1 week off and 2 weeks on for PLX3397 doses during the 3-week pembrolizumab dosing interval) and/or the same dose level with a run in period of PLX3397 for two weeks prior to starting pembrolizumab. Subjects who complete the Dose-escalation Phase may continue in the study at the dose determined for their cohort, assuming that dose is considered pharmacodynamically active. Also, these subjects can be titrated up to the RP2D, at the discretion of the Investigator. **Expansion Phase:** Subjects with any 1 of the tumor types will receive pembrolizumab 200 mg IV every 3 weeks in combination with oral PLX3397 administered as a split dose at the RP2D of PLX3397.
Study Endpoints:	**Primary Endpoint** • To establish the recommended RP2D and schedule of the combination of pembrolizumab and PLX3397, i.e., the MTD or MAD, for future trials. The MTD is defined as the dose level below the one at which more than 1 of 6 subjects experience DLT in Cycle 1 (1 cycle = 42 days). The planned MAD is defined as PLX3397 administered orally at 1000 mg/day as a split dose. **Secondary Endpoints** • To evaluate the safety and tolerability of the combination of pembrolizumab and PLX3397, based on the incidence of AEs, as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). • To evaluate ORR by RECISTv1.1 guidelines, relative to the assumed historical control rate for pembrolizumab, for each of the tumor types in subjects treated with the RP2D of PLX3397 for the combination of PLX3397 and pembrolizumab (Expansion Phase). Subjects with each of the tumor types will also be analyzed by RECISTv1.1 for PFS. **Exploratory Endpoints** • To evaluate ORR by irRECIST guidelines, relative to the assumed historical control rate for pembrolizumab, for each of the tumor types in subjects treated with the

	RP2D of PLX3397 for the combination of PLX3397 and pembrolizumab (Expansion Phase). Subjects with each of the tumor types will also be analyzed by irRECIST for PFS. • To evaluate ORR and PFS by RECISTv1.1 guidelines descriptively by cohort for subjects in the Dose-escalation Phase. • To determine effects of the combination of PLX3397 and pembrolizumab on multiple biomarkers of disease or treatment, through analysis of available paired tumor biopsy samples using methods that include but are not limited to Nanostring and IHC of intratumoral CD68+ macrophages and CD8+ T-cells. Optional baseline and 28-day post-treatment biopsies will be collected in the Dose-escalation phase and will be mandatory in the Expansion Phase, unless deemed medically unsafe by the Investigator.
Statistical Analyses:	The Dose-escalation Phase of the study will employ a standard 3+3 design in order to determine the R2PD for PLX3397 when administered with pembrolizumab 200 mg IV every 3 weeks. The DLT-window is 1 cycle (42 days). Up to seven dose levels or regimens of PLX3397 will be investigated. Subjects will be treated in cohorts of 3 to 6, and the dose level will be escalated if the clinical toxicity is acceptable. The safety and tolerability of the combination of pembrolizumab and PLX3397 will be assessed by the incidence of AEs as graded by the NCI CTCAE. For the Expansion Phase, efficacy will be evaluated separately within each cohort based on tumor type. A truncated sequential probability ratio test for single-arm binary response studies will be employed in each of these cohorts (DOD RAC 2005). This sequential monitoring procedure establishes continuous boundary conditions to stop enrollment for either efficacy or futility at any time up to the total prescribed sample size. Disease response will be evaluated using RECISTv1.1 criteria on the Efficacy Analysis Set. Overall response rate (ORR), defined as the proportion of subjects who achieve a best disease response of either CR or PR, will be evaluated. Patients who discontinue study therapy due to clinical progression, radiographic progression or death without the required tumor assessments will be considered to be non-responders in the ORR calculation. The efficacy analysis will

	include all subjects with baseline tumor measurements who received at least on dose of study treatment. The point estimate, confidence interval, and adjusted p-values for testing whether the observed ORR is statistically greater than the specified null rate will be provided for each cohort. Exact methods for binary, sequential data will be employed for the analysis. A one-sided alpha of 0.05 and 80% power will be used for all tumor types for calculating stopping boundary conditions.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration–time curve
AUC_{0-6}	Area under the plasma concentration–time curve from time zero to 6 hours
β-hCG	beta human chorionic gonadotropin
BID	Twice daily
BRAF	V-Raf murine sarcoma viral oncogene homolog B
CCRCC	Clear cell renal carcinoma
CI	Confidence interval
crcl	Creatinine clearance
C_{max}	Peak plasma concentration
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CSF1	Colony stimulating factor 1
CSF1R	Receptor for colony stimulating factor 1
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DLT	Dose-limiting toxicity
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal Growth Factor Receptor
FDA	US Food and Drug Administration
FDG-PET	FDG-PET= [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography-computer tomography (PET/CT)
FMS	(See CSF1R)

Abbreviation	Definition
GBM	Glioblastoma multiforme
GGT	Gamma-Glutamyl Transferase
GIST	Gastrointestinal stromal tumor
GCP	Good Clinical Practice(s)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IHC	Immunohistochemistry
INR	International normalized ratio
[int]	Intermittent
ITD	Internal tandem duplications
IRB	Institutional review board
irRECIST	Immune-related RECIST
MAD	Maximum administered dose
MDSC	Myeloid-derived suppressor cells
MRI	Magnetic resonance imaging
msec	Millisecond
MTD	Maximal tolerated dose
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluated
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PD	Progressive disease
PDA	Pancreatic ductal adenocarcinoma
PEG tube	Percutaneous endoscopic gastrostomy tube
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PO	Oral
PR	Partial response
PT	Prothrombin time
QD	Once daily
QPCR	Quantitative polymerase chain reaction
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's formula

Abbreviation	Definition
RBC	Red blood cell
RP2D	Recommended phase 2 dose
RECISTv1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SCF	Stem cell factor
SD	Stable disease
T_{max}	Time to peak plasma concentration
TNBC	Triple Negative Breast Cancer
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Investigational Product

1.1.1. PLX3397

PLX3397 is a novel, orally active, small molecule inhibitor intended for oral administration that targets 3 kinases: 1) FMS (also referred to as CSF1R, the receptor for colony stimulating factor 1 [CSF1, also known as macrophage-colony stimulating factor] as well as the ligand interleukin 34 [IL-34]); 2) Kit, the receptor for stem cell factor (SCF); and 3) oncogenic Flt3, the receptor for Flt3 ligand. However, it otherwise remains highly selective in terms of impact on the activity of other receptors and kinases. The potent inhibition of these 3 kinases can be exploited to attack tumors through a variety of mechanisms: 1) direct inhibition of inhibiting oncogenic drivers such as oncogenic Kit and Flt3 mutant proteins; 2) inhibition of paracrine loops between stromal cells and tumors; 3) blockade of migration and angiogenesis, 4) blockage of CSF1-dependent myeloid-derived suppressor cells; and 5) disruption of osteolytic metastases.

An important role for tumor-infiltrating macrophages in tumor progression has pointed to FMS as a key target in multiple tumor types (Coffelt 2009). The pro-tumorigenic role of CSF1 and FMS is supported by a wealth of studies demonstrating that CSF1 levels predict a poor outcome in a variety of oncology indications, including breast, ovarian, non-small cell lung, and colorectal cancers. Further strengthening the fundamental tumorigenic role of FMS is a key study showing that mice defective in CSF1 are protected against tumor metastases (Lin 2001). For details, please refer to the PLX3397 Investigator's Brochure.

1.1.2. Intended Use Under Investigation

PLX3397, a CSR-1R inhibitor, in combination with pembrolizumab, an anti-PD-1 antibody, is under investigation for the treatment of subjects with advanced melanoma and other solid tumors.

1.2. Nonclinical Studies

1.2.1. Nonclinical Studies with PLX3397

The effects of PLX3397 on multiple aspects of tumorigenesis have been characterized in cellular and in vivo assays. The proliferation of cell lines that depend on CSF1, SCF, or endogenous Flt3-ITD (internal tandem duplications) is inhibited by 50% (IC_{50}) at drug concentrations of less than 1 μM. Furthermore, CSF 1 induced autophosphorylation of FMS and SCF-induced autophosphorylation of Kit are potently inhibited by PLX3397. Finally, the RANK-L- and CSF 1 dependent differentiation of osteoclast precursors is also potently inhibited by PLX3397. These in vitro results translate to PLX3397 effects in a variety of in vivo models for FMS-dependent proliferation, FMS-dependent osteoclast differentiation, Flt3-ITD dependent tumor growth, and Kit-dependent mast cell proliferation.

While pharmacologic effects due to the inhibition of FMS, Kit and oncogenic Flt3 are expected, the relative selectivity of PLX3397 against other kinases suggests that off-target effects against other kinases should be limited.

Additional detailed information regarding the nonclinical pharmacology and toxicology of PLX3397 can be found in the PLX3397 Investigator's Brochure.

1.2.2. Nonclinical Studies with PLX3397 and PD-1 Antibody

Mobilizing the body's immune system to fight cancer is a promising approach to induce durable responses. In particular, cytotoxic T-cells play a central role in immune-mediated control of cancer. By recognizing tumor specific antigens, T-cells are able to specifically detect and eliminate cancer cells. Thus, immune escape, the multiple mechanisms a tumor uses to escape from immune-mediated rejection, is one of the hallmarks of cancer. In recent clinical trials, agents that block the inhibitory receptors (e.g., PD-1 and CTLA4) on T-cells have demonstrated survival benefit in a subset of cancer patients, despite advanced disease. The immunosuppressive nature of the tumor microenvironment is a factor that limits wider clinical benefit of immune checkpoint blockade. Harnessing the full potential of cancer immunotherapy requires coordinated strategies to mitigate immunosuppression. The main drivers of immune escape include tumor-associated macrophages (TAM) and myeloid-derived suppressor cells. These cells not only mediate immune suppression but also promote metastasis and induce resistance to chemotherapy and radiation. However, inhibition of FMS, the pivotal myeloid growth factor receptor, can functionally reprogram the tumor microenvironment to eliminate tumor infiltrating macrophages and promote productive antitumor T-cell responses.

This potential synergy between CSF1R inhibitor (PLX3397) and immune checkpoint inhibitors has been evaluated in a mouse model of pancreatic ductal adenocarcinoma (PDAC) (Zhu 2014). PD-1 and CTLA4 antagonists have shown limited efficacy as single agents to suppress PDAC growth. However, combining these agents with PLX3397 and other FMS blockades has potently elicited tumor regression. As expected, CSF1R inhibition decreases myeloid responses in the stromal compartment and alters the function of TAMs and dendritic cells to support T-cell-mediated antitumor immunity.

1.3. Clinical Experience

1.3.1. PLX3397 Clinical Pharmacokinetics

Exposure to PLX3397 has been evaluated in 8 clinical studies. PLX3397 was administered as single agent in 5 studies and in combination with paclitaxel, temozolomide, or vemurafenib in 3 studies. The PK of PLX3397 at dose levels between 200 mg/day and 1200 mg/day was evaluated in the dose-escalation and extension study, PLX108-01, using once daily (QD) or twice daily (BID) dosing in the fasting state. The time to peak plasma concentration (T_{max}) is approximately 2 hours, and the mean accumulation ratio compared to Day 1 values is approximately 2-fold. In general, there is dose-proportional exposure. In the PLX108-05 acute myeloid leukemia dose-escalation study at dose levels between 800 mg/day and 5000 mg/day, saturation of exposure was observed at 3000 mg/day.

The steady state exposure of 900 mg/day (QD) cohort in PLX108-03 Hodgkin's lymphoma study and of 1000 mg/day (BID) cohorts in all the other single agent studies (PLX108-04 glioblastoma, PLX108-05 AML, PLX108-06 prostate cancer) were similar to the exposure of the respective dose groups in PLX108-01 Solid tumors study.

The mean PLX3397 plasma concentrations for the 800 mg/day (BID) cohorts at 2, 4, and 6 hours in the combination studies with paclitaxel (PLX108-07), temozolomide (PLX108-08), and vemurafanib (PLX108-09) were comparable to those seen in PLX3397 single agent studies.

Subjects administered a single dose of 600 mg of PLX3397 with a high-fat, high-calorie meal displayed an approximately 2-fold increase in peak plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) compared with subjects administered PLX3397 in the fasted state (PLX108-11). When PLX3397 was administered in the presence of esomeprazole, overall exposure was reduced approximately 30%.

1.3.2. PLX3397 Clinical Safety

As of 30 June 2014, data are available on 345 subjects who have been enrolled in the PLX3397 clinical program across 8 clinical studies: PLX108-01, PLX108-03, PLX108-04, PLX108-05, PLX108-06, PLX108-07, PLX108-08, and PLX108-09. Of the 345 subjects, 181 subjects with solid tumors received PLX3397 as a single agent (which included advanced, incurable, solid tumors; relapsed or refractory Hodgkin's lymphoma; recurrent glioblastoma multiforme; or progressive castration resistant prostate cancer with high circulating tumor cell counts). Ninety subjects received PLX3397 as a single agent for relapsed or refractory AML. Seventy-four subjects received PLX3397 in combination with other therapies. Most of these studies are ongoing.

The most frequently reported treatment-emergent adverse events (>20% of subjects) among all treated subjects included fatigue, nausea, decreased appetite, diarrhea, anemia, vomiting, and increases in aspartate aminotransferase (AST). Hair color changes (depigmentation) and constipation also commonly occurred in solid tumor subjects receiving single agent PLX3397. With the exception of febrile neutropenia (which occurred at a high rate in the AML study), less than 10% of these common adverse events (AEs) were considered as Grade 3 or higher.

Treatment-related serious adverse events (SAEs) reported more than once included neutropenia (including febrile neutropenia), anemia, pneumonia, increased AST or ALT, increased international normalized ratio (INR), dehydration, hyponatremia, and maculo-papular rash.

During the Dose-escalation Phase of this study, preliminary analyses show the following: one cohort was studied at 600 mg total daily dose of PLX3397 in combination with pembrolizumab. Two liver-related DLTs were observed, both in subjects with liver metastases. One subject entered the study with Grade 2 AST that worsened to Grade 3 at C1D8; the subject stopped PLX3397 and terminated the study due to rapid disease progression. The second subject entered the study with normal transaminases, experienced Grade 3 elevation at C2D8 that resolved; after a short rechallenge with

PLX3397, the subject had disease progression and terminated the study. Amendment 1 was instituted that excluded liver metastases and excluded Grade 2 transaminase elevations at screening. The next cohort was enrolled at 400 mg total daily dose of PLX3397 in combination with pembrolizumab and 3 subjects completed the 42-day DLT window without any DLTs. Re-escalation to 600 mg total daily dose of PLX3397 in combination with pembrolizumab in 11 evaluable subjects with and without liver metastasis and with normal transaminases at study entry resulted in no DLTs. Cohorts of 800 mg total daily dose of PLX3397, either continuous or intermittent, in combination with pembrolizumab in subjects without liver metastasis showed 4 liver-related DLTs out of 9 evaluable subjects. Thus the recommended phase 2 dose (RP2D) of PLX3397 in combination with pembrolizumab was determined to be 600 mg/day (as a split dose, 200 mg in the morning and 400 mg in the evening) based on the incidence of observed toxicities (i.e., ≥2 patients with DLT at the 800 mg total daily dose level) and overall tolerability.

1.3.3. Pembrolizumab in Clinical Trials

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator Brochure.

1.4. Study Rationale

Many patients who do not respond to conventional anticancer therapies lack intratumoral and invasive margin infiltration by T-cells, most likely due to a tumor microenvironment that inhibits the activity of antitumor T-cells. Prominent in this tumor microenvironment are immune suppressive macrophages that serve as an “invisibility cloak,” precluding activation of antitumor T-cells.

In an animal model, specific depletion of immune suppressive macrophages with PLX3397, a small molecule inhibitor of the CSF1R inhibitor, resulted in increased intratumoral accumulation and function of antigen-specific CD8+ T-cells (Mok 2014). Additionally, analysis of over 100 melanoma biopsies of patients receiving pembrolizumab, an anti-PD-1 antibody, allowed understanding of the critical role of intratumoral CD8+ T-cells in mediating the antitumor responses achieved with this therapy (Tumeh 2014).

Based on these data, Plexxikon proposes to conduct a Phase 1/2a trial combining the CSF1R inhibitor PLX3397 with the anti-PD-1 antibody pembrolizumab. The rationale is that combined administration of these agents will inhibit the immunosuppressive macrophages that mask cancer cells and activate T-cell responses to them.

In subjects with melanoma and other solid tumors who have relapsed from or are refractory to treatment, it is hoped that this process will result in tumor regression, improved survival, and measurably improved quality of life. The primary objective of the study is determination of safety; analyses of clinical activity will focus on the anticipated effects of depletion of intratumoral immune suppressive macrophages, which is believed will result in improved number and functionality of intratumoral CD8+ T-cells.

1.5. Benefits and Risks for Study Subjects

PLX3397 in combination with pembrolizumab may provide an alternative therapy for subjects with metastatic melanoma/solid tumors.

Risks of treatment with PLX3397 include bone marrow suppression and elevations of liver transaminases and bilirubin.

In uncontrolled clinical studies of single-agent PLX3397 and in combination with other anticancer agents, bone marrow suppression with leukopenia (neutropenia and/or lymphopenia), anemia and thrombocytopenia, either alone or with pancytopenia, has been observed. Therefore, subjects will be monitored closely for clinically significant reduction of neutrophils, serum hemoglobin, or platelet counts, and should this condition arise, standard of care supportive measures will be initiated, including broad spectrum antibiotics, as appropriate.

In addition, elevations of liver transaminases and bilirubin have also been observed in studies with PLX3397. Protocol-defined dose reductions and discontinuations of PLX3397, increased frequency of laboratory monitoring, and reporting of findings will be performed, as appropriate. Rechallenge with PLX3397 will not be attempted without prior discussion with the Plexxikon Medical Monitor.

For additional descriptions of risks and benefits, see the Plexxikon PLX3397 Investigator's Brochure, Section 6, Summary of Data and Guidance for the Investigator.

Risks of treatment with pembrolizumab include immune-mediated conditions, specifically, pneumonitis, colitis, hypophysitis, and nephritis, hyperthyroidism, hypothyroidism; renal failure; other immune-mediated adverse reactions; and embryofetal toxicity. See the Keytruda Package Insert and the Pembrolizumab Investigator's Brochure.

Despite the potential benefits of combination treatment of PLX3397 and pembrolizumab described above, the combination could further heighten the risks of immune-mediated disease.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

- To establish the recommended phase 2 dose (RP2D) and schedule of PLX3397 for the combination of PLX3397 and pembrolizumab.

- To determine the safety and tolerability of the combination the CSR-1R inhibitor PLX3397 and the anti-PD-1 antibody pembrolizumab.

2.1.2. Secondary Objectives

- To define the AE profile of the combination of PLX3397 and pembrolizumab and to determine the relationship of AEs to study treatment.
- To evaluate the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECISTv1.1) guidelines (Appendix 17.4), relative to the assumed historical control rate for pembrolizumab, for each of the tumor types in subjects treated with the RP2D of PLX3397 for the combination of PLX3397 and pembrolizumab (Expansion Phase). Subjects with each of the tumor types will also be analyzed by RECISTv1.1 for progression-free survival (PFS)

2.1.3. Exploratory Objectives for Dose-escalation and Expansion Phases

- To evaluate biomarkers of drug effects on liver.
- To evaluate biomarkers of treatment effects, including but not limited to myeloid-derived suppressor cell function.
- To evaluate ORR by immune-related RECIST (irRECIST), relative to the assumed historical control rate for pembrolizumab in subjects treated with the RP2D for the combination of PLX3397 and pembrolizumab (Expansion Phase).
- To determine effects of the combination of PLX3397 and pembrolizumab on multiple biomarkers of disease or treatment, through analysis of available paired tumor biopsy samples using methods that include but are not limited to Nanostring and IHC of intratumoral CD68+ macrophages and CD8+ T-cells. Mandatory baseline (up to -2 days) and 28-day (± 3 days) post-treatment biopsies will be collected in the Expansion Phase, unless deemed medically unsafe by the Investigator. Biopsies will be optional in the Dose-escalation Phase.

2.2. Study Hypothesis

The null hypothesis (applicable to the secondary objective, determination of ORR) is that the combination treatment of PLX3397 and pembrolizumab in subjects with advanced melanoma and other solid tumors who have relapsed from or are refractory to treatment, results in no difference in tumor regression than historical data observed with single-agent pembrolizumab.

3. STUDY DESIGN

3.1. Overview of the Study Plan

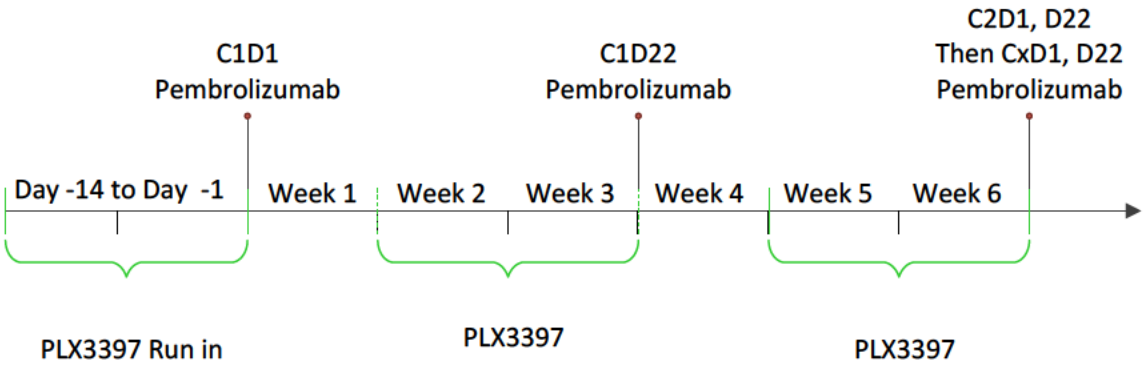
3.1.1. Design and Treatments

This is a Phase 1/2a, 2-part, open-label, clinical trial. The first part comprises a Dose-escalation Phase, which uses a standard 3+3 design. During this part of the study, subjects receive pembrolizumab 200 mg IV every 3 weeks in combination with a starting dose of oral PLX3397 at 600 mg/day (administered twice daily as a split dose of 200 mg in the morning and 400 mg in the evening), with sequential escalations to 800 and 1000 mg/day. (If the 600 mg/day dose of PLX3397 is not well tolerated, de-escalation to 400 mg/day will be allowed.)

The goal of this phase is to determine the RP2D of PLX3397, defined as the maximum tolerated dose (MTD) or maximum administered dose (MAD) of PLX3397. The MTD is defined as the dose level below the one at which more than 1 of 6 subjects experience a dose-limiting toxicity (DLT) in Cycle 1 during the 42-day DLT window. If the MTD cannot be determined due to lack of DLT during the 42-day DLT window, the MAD of PLX3397 will be declared the RP2D. The MAD is defined as the maximum dose administered during the study (Table 1), i.e., PLX3397 administered orally at 1000 mg/day (as a split dose). The RP2D will be confirmed with at least 6 subjects. Subjects who complete the Dose-escalation Phase may continue in the study and receive treatment at the dose assigned to their cohort, assuming that dose is considered pharmacodynamically active, or these subjects can be titrated up to the RP2D at the discretion of the Investigator.

An intermediate dose level may be studied and may be comprised of alternative dosing regimens such as intermittent dosing (e.g., 1 week off and 2 weeks on for PLX3397 doses during the 3 week pembrolizumab dosing interval) and/or the same dose level with a run in period of PLX3397 for two weeks prior to starting pembrolizumab (see Figure 1).

Figure 1: Graphic Representation of Intermittent Dosing with Optional PLX3397 Run-in



The second part comprises an Expansion Phase, which uses a truncated sequential probability ratio test for single-arm binary response studies. Subjects with any 1 of the tumor types (Table 2) will receive pembrolizumab 200 mg IV every 3 weeks in combination with oral PLX3397 administered twice daily as a split dose at the RP2D of PLX3397. Dosing will continue until a subject experiences disease progression as determined by irRECIST, unacceptable toxicity, or meets any other discontinuation criterion.

Throughout the study, dose decrements of 200 mg/day of PLX3397 are permitted for management of toxicity (Table 3).

3.1.1.1. Dose-escalation Phase

During the Dose-escalation Phase, up to 42 subjects with advanced solid tumors (any type) will be enrolled sequentially in up to 7 cohorts of 3 to 6 subjects using a standard 3+3 design. Each cohort represents a different dose or regimen. Subjects will receive pembrolizumab 200 mg IV in combination with oral PLX3397, in combination with a starting dose of PLX3397 at 600 mg/day, with sequential escalations to 800 and 1000 mg/day. (If the 600 mg/day dose of PLX3397 is not well tolerated, de-escalation to 400 mg/day will be allowed.) If 400 mg/day is tolerated (i.e., no DLTs in 3 subjects or ≤1 DLT in 6 subjects), then re-escalation to 600 mg/day may be considered within the hepatic laboratory test limits in inclusion #10. Further dose escalation will be considered depending upon safety and tolerability of each cohort. PLX3397 is administered twice daily as a split dose. (See Section 3.2.1, which provides the rationale for PLX3397 dosing).

If a DLT is observed during the 42-day DLT window in 1 subject in a given cohort, at least 6 subjects will be treated at that dose. If DLT is observed in 2 or more of 6 subjects at a dose level, then this dose level will have exceeded the 33% DLT rate, and the next lower dose level will be tested to have a total of at least 6 subjects with ≤1 DLT and be defined as the MTD. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 42 days. If PLX3397 1000 mg/day, orally administered twice daily as a split dose, in combination with pembrolizumab 200 mg IV, every 3 weeks, is not the MTD, no further dose escalation will be conducted, and this dose level will be the defined MAD after observation of at least 6 subjects during the DLT window. After completion of the Dose-escalation Phase, all safety and tolerability data will be reviewed and the RP2D (i.e., MTD/MAD) will be determined.

Subjects who complete the Dose-escalation Phase may continue in the study and receive treatment at the dose determined for their cohort, assuming that dose is considered pharmacodynamically active. Also, these subjects can be titrated up to the RP2D, at the discretion of the Investigator.

Table 1. Treatments During the Dose-escalation Phase of Study PLX108-14

Dose Cohort[a]	Number of Subjects	Starting Dose of PLX3397[b]	Pembrolizumab
[int] (if needed)[d]	3 (+ 3)	400, 600 or 800 mg/day orally	200 mg IV every 3 weeks
[-1] (if needed)	3 (+ 3)	400 mg/day orally[c]	200 mg IV every 3 weeks
1	3 (+ 3)	600 mg/day orally	200 mg IV every 3 weeks
2	3 (+ 3)	800 mg/day orally	200 mg IV every 3 weeks
3	3 (+ 3)	1000/day orally	200 mg IV every 3 weeks

IV = intravenous

[a] Cohort numbering is an example and may vary depending on the dose levels and regimens that are studied.

[b] Throughout the study, dose decrements of 200 mg/day of PLX3397 are permitted for management of toxicity.

[c] If the dose of 600 mg/day is not well tolerated, a dose cohort starting at 400 mg/day may be employed.

[d] Intermittent regimen: PLX3397will begin 7 days after pembrolizumab administration and continue for 14 days until the next pembrolizumab dose throughout the course of the study. A run-in of up to 2 weeks with PLX3397 is optional. PLX3397 dose will be determined by the Cohort 1–3 dose if DLT are observed (see Section 3.1.7.2 and Figure 1).

3.1.1.2. Expansion Phase

During the Expansion Phase, additional subjects with advanced solid tumors of any 1 of the tumor types summarized in Table 2 will be enrolled into the study and receive the RP2D of PLX3397 (administered twice daily as a split dose) in combination with pembrolizumab 200 mg IV every 3 weeks. Dosing will continue until a subject experiences disease progression as determined by irRECIST, unacceptable toxicity, or meets any other discontinuation criterion such as meeting criteria for complete response (CR). Enrollment into each tumor type may occur simultaneously or in a staggered fashion.

Table 2. Tumor Types Investigated in the Expansion Phase of PLX108-14

Tumor Types	Maximum Total Sample Size[b]
Advanced melanoma: anti-PD-1/PD-L1 naïve and CSF1R naïve	23
Advanced melanoma: prior anti-PD-1/PD-L1 therapy but never responded	33
Advanced melanoma: prior anti-PD-1/PD-L1 therapy and responded but later progressed as defined by irRECIST while on therapy	33
NSCLC (non-squamous; EGFR and ALK wild-type showing primary progression with anti-PD1/anti-PDL1 therapy)	33
Ovarian	33
TNBC	38
SCCHN Showing primary progression with anti-PD1/anti-PDL1 therapy	33
Clear cell renal cell carcinoma (CCRCC)	48
PDA	33
Gastric	39
Glioblastoma multiforme (GBM)	33
GIST	33
High grade soft tissues sarcoma[a]	38
Cholangiocarcinoma	33
Total	**483**

irRECIST = immune-related Response Evaluation Criteria in Solid Tumors (see irRECIST Tip Sheet provided in the Study Reference Manual); NSCLC = non-small cell lung cancer;
PDA = pancreatic ductal adenocarcinoma; SCCHN = squamous cell carcinoma of the head and neck;
GIST=gastrointestinal stromal tumor; TNBC = triple-negative breast cancer;

[a] High grade soft tissue sarcoma includes undifferentiated pleomorphic sarcoma and liposarcoma.

[b] Subjects must be naïve to anti-PD1/PDL1 inhibitors unless otherwise noted.

3.1.1.3. Dose Decrements

Throughout the study, dose decrements of 200 mg/day of PLX3397 are permitted for management of toxicity (see Table 1 and Table 3).

3.1.2. Study Sites

The Dose-escalation Phase will be conducted at up to 5 study sites in the US. Additional sites may be added for the Expansion Phase.

3.1.3. Study Population

Adult subjects (≥18 years of age) with histologically confirmed Stage III or Stage IV metastatic melanoma or solid tumors are eligible. Subjects enrolled in the Dose-escalation Phase could have any type of solid tumor and could have previously received an anti-PD-1 or anti-PD-L1 antibody or could be naïve to both these therapies.

Subjects enrolled in the Expansion Phase should have one of the tumor types and pretreatment requirements specified in Table 2.

3.1.4. Study Endpoints

3.1.4.1. Primary Endpoint

- To establish the recommended RP2D and schedule of the combination of pembrolizumab and PLX3397, i.e., the MTD or MAD, for future trials. The MTD is defined as the dose level below the one at which more than 1 of 6 subjects experience DLT in Cycle 1 (1 cycle = 42 days). The planned MAD is defined as PLX3397 administered orally at 1000 mg/day as a split dose (Table 1).

3.1.4.2. Secondary Endpoints

- To evaluate the safety and tolerability of the combination of pembrolizumab and PLX3397, based on the incidence of AEs, as graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, (CTCAE).
- To evaluate ORR by RECISTv1.1 guidelines (Appendix 17.4), relative to the assumed historical control rate for pembrolizumab, for each of the tumor types in subjects treated with the RP2D of PLX3397 for the combination of PLX3397 and pembrolizumab (Expansion Phase). Subjects with each of the tumor types will also be analyzed by RECISTv1.1 for PFS.

3.1.4.3. Exploratory Endpoints

- To evaluate ORR by irRECIST guidelines (see the irRECIST Tip Sheet, provided in the Study Reference Manual), relative to the assumed historical control rate for pembrolizumab, for each of the tumor types in subjects treated with the RP2D for the combination of PLX3397 and pembrolizumab. Subjects with each of the tumor types will also be analyzed by irRECIST for PFS.
- To evaluate ORR and PFS by RECISTv1.1 guidelines (Appendix 17.4) descriptively by cohort for subjects in the Dose-escalation Phase.
- To determine effects of the combination of PLX3397 and pembrolizumab on multiple biomarkers of disease or treatment, through analysis of available paired tumor biopsy samples using methods that include but are not limited to Nanostring and IHC of intratumoral CD68+ macrophages and CD8+ T-cells. Paired biopsies are optional in Dose-escalation and mandatory in the Expansion Phase, unless deemed medically unsafe by the Investigator.

3.1.5. Duration of the Study

It is estimated that it will take approximately 12 months to complete the Dose-escalation Phase and up to 2 years to enroll subjects in and subsequently complete the Expansion Phase.

3.1.6. Duration of Subject Participation

Subjects who complete a maximum number of 16 cycles (approximately 24 months; 1 cycle = 42 days) on study treatment and demonstrate clinical benefit with manageable toxicity will stop both Study Drugs.

3.1.7. Modifications and Rules During the Dose-escalation Phase (i.e., the 42-day DLT Observation Period)

DLTs are defined in Section 3.1.7.1. Dose-escalation rules, based on the principles underlying the standard 3+3 design, are provided in Section 3.1.7.2. The definition of the MTD is provided in Section 3.1.7.3.

3.1.7.1. Dose-Limiting Toxicities

A DLT is defined as any AE that is temporally related to Study Drug administration and is not due to the subject's underlying malignancy and for which there is no clear evidence for an alternative etiology, and that meets one of the following NCI CTCAE criteria during the first 42 days of Study Drug administration (the "DLT observation period"):

- Hematologic Toxicities
  - Grade 4 anemia
  - Grade 3 or 4 neutropenia lasting ≥7 days
  - Grade ≥3 neutropenia with fever
  - Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with clinically significant bleeding
- Other Toxicities
  - Any other Grade ≥3 toxicity despite adequate supportive care except for the following:
    - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤1 within 7 days, with or without appropriate supportive therapy
    - Grade ≥3 rash that resolves to Grade ≤2 within 7 days
    - Grade 3 fatigue that resolves to ≤Grade 2 within 14 days
    - Grade ≥3 laboratory abnormalities that, in the judgment of the Investigator are not clinically significant
  - As judged by Investigator and Medical Monitor, a high rate of missed doses if related to an AE. Study Drug interruption longer than 14 days (or permanent discontinuation) for a persistent drug-related AE will be considered a DLT, irrespective of severity.

Use of hematopoietic growth factors during the DLT period requires approval by the Medical Monitor.

3.1.7.2. Rules for Dose Escalation

The study is designed to reduce the chance of escalating the dose when the probability of DLT is high and to increase the chance of escalating the dose when the probability of DLT is low. The rules for dose escalation, based on the standard 3+3 design, are provided below:

- If none (0) of the initial 3 subjects in a cohort experiences a DLT, then a new cohort of 3 subjects will be treated at the next higher dose level.
- If 1 of 3 subjects in a cohort experiences a DLT, then up to 3 additional subjects will be treated at the same dose. Escalation will continue if no more than 1 of 6 subjects experiences a DLT.
- If 2 or more subjects in a cohort experience a DLT, then the MTD will have been exceeded, and no further dose escalation will occur. The previous dose level will be considered the MTD or an intermediate dose level may be introduced.
- If only 3 subjects were treated at a dose level under consideration as the MTD, then up to 3 additional subjects will be accrued. If no more than 1 of 6 subjects treated at the dose level under consideration as the MTD experiences a DLT, then that dose level will be confirmed as the MTD. If 2 or more subjects in that cohort experience a DLT, then the previous or an intermediate dose level will be studied in the same fashion.
- If PLX3397 1000 mg (given orally twice daily as a split dose) and pembrolizumab 200 mg given IV every 3 weeks is not the MTD, no further dose escalation will be conducted and this dose level will be defined as the MAD and hence the RP2D after observation of at least 6 subjects during the DLT window.

An intermediate dose level may comprise alternative dosing regimens such as intermittent dosing (e.g., 1 week off and 2 weeks on for PLX3397 doses during the 3-week pembrolizumab dosing interval; see Appendix 17.7) and optionally with the same dose level with a run in period of PLX3397 for 2 weeks prior to starting pembrolizumab (see Appendix 17.8). See Figure 1 for graphical representation of alternate dosing regimens. Another alternative regimen may be 5 days on and 2 days off. For all regimens, the cumulative 3-week PLX3397 exposure may not exceed the dose level where 2 or more subjects experienced a DLT. For example, if 800 mg/day continuous dosing of PLX3397 results in 2 or more subjects experiencing a DLT, then an intermediate dose level of 1 week off and 2 weeks on 800 mg/day PLX3397 may be studied. The intermediate dose level or regimen will be determined by the Sponsor and Investigators based on the totality of available safety, pharmacodynamics and pharmacokinetic data.

If the Sponsor and Investigators determine that, in the absence of DLTs, enrollment of additional subjects is required to better determine PK or safety, enrollment of an additional 3 or more subjects may be undertaken at one or more of the dose levels already studied, including intermediate doses.

3.1.7.3. Maximum Tolerated Dose

The MTD is defined as the dose level below the one at which more than 1 of 6 subjects experience DLT in Cycle 1.

3.1.8. Dosing Interruptions During Both Phases of the Study

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

3.1.9. Guidelines for Management of Potential Toxicities Associated with PLX3397 and Pembrolizumab

Guidelines for management of potential PLX3397-associated toxicities are summarized in Section 3.1.9.1 and for pembrolizumab-associated toxicities in Section 3.1.9.2. All guidelines presented below apply to both phases of the study (Dose-escalation and Expansion). However, if during the Dose-escalation Phase any toxicity qualifies as a DLT (see Section 3.1.7.1); the guidelines for determining the MTD should be followed (see Section 3.1.7.3).

In those instances in which a possible drug-related toxicity requires dose modification, and it is unclear which agent is more likely be responsible, both compounds should be interrupted and the dose modification guideline for each should be followed.

3.1.9.1. Potential PLX3397 Toxicities and Guidelines for Management

Reductions or interruptions of the dose for toxicity may take place at any time during the study according to the guidelines in Table 3 and Table 4. Dose reduction/interruption guidelines for hematologic and nonhematologic treatment-related TEAEs are based on severity. Dose interruptions can be implemented at the discretion of the treating Investigator to manage intolerable or clinically significant toxicity. If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study drug delay, with the exception of PK assessments, which should be deferred until treatment is resumed. Interruptions due to toxicity lasting >3 weeks require treatment discontinuation unless the medical monitor approves continuation.

Table 3 provides guidelines for the management of PLX3397-related toxicities. Dose reductions for management of toxicity should occur in decrements indicated in Table 3, depending on the toxicity grade shown in the table. These parameters are only a guide and are not intended to supersede the clinical judgment of the treating physician. Table 4 provides guidelines for the management of PLX3397-related liver toxicities.

All adjustments should be made in consultation with the Medical Monitor.

Table 3. PLX3397-related Toxicities and Guidelines for Management, Excluding Hepatic Toxicities

Toxicity Grade (CTCAE) or Toxicity Description	PLX3397 Dose Changes During Current Treatment Period[a]	Dose Adjustments for Resumption of Treatment[a]
Hematologic Toxicities		
Grade 3 or Grade 4 neutropenia		
1st Appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L.	If recovered to ANC $\geq 1 \times 10^9$/L in ≤7 days, resume at same dose.
		If ANC does not recover to $\geq 1 \times 10^9$/L after 7 days, reduce dose by 200 mg.
2nd Appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L.	If recovered to ANC $\geq 1 \times 10^9$/L in ≤7 days, reduce dose by 200 mg.
		If ANC does not recover to $\geq 1 \times 10^9$/L after 7 days, reduce dose by an additional 200 mg.
3rd Appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L.	If recovered to ANC $\geq 1 \times 10^9$/L in ≤7 days, reduce dose by 200 mg.
		If ANC does not recover to $\geq 1 \times 10^9$/L after 7 days, discontinue permanently.
4th Appearance	Discontinue Permanently	NA
Grade 3 or Grade 4 febrile neutropenia		
1st Appearance	Interrupt until ANC and fever recover.	Once resolved to ANC $\geq 1 \times 10^9$/L and T ≤38°C, reduce dose by 200 mg per day.
2nd Appearance	Interrupt until ANC and fever recover.	Once resolved to ANC $\geq 1 \times 10^9$/L and T ≤38°C, reduce dose by an additional 200 mg.
3rd Appearance	Discontinue permanently.	NA
Grade 4 thrombocytopenia		
1st Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	Reintroduce at same dose
2nd Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If PLT does not recover to $\geq 75 \times 10^9$/L after 7 days, reduce dose by 200 mg.
3rd Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	Reduce dose by an additional 200 mg.
4th Appearance	Discontinue permanently.	NA
Other Related Toxicities (≥Grade 3), with the exceptions of liver-enzyme abnormalities (for which, see Tables 4 and 5 below).		
Other Related Grade 3 (start symptomatic treatment when possible)		
1st Appearance	Interrupt until resolved (Grade 0–1).	If recover <5 days, resume at same dose. Reduce by 200 mg if symptoms persist for ≥5 days despite supportive management.
2nd Appearance	Interrupt until resolved (Grade 0–1).	Reduce by an additional 200 mg.

Toxicity Grade (CTCAE) or Toxicity Description	PLX3397 Dose Changes During Current Treatment Period[a]	Dose Adjustments for Resumption of Treatment[a]
3rd Appearance	Discontinue permanently.	NA
Other Related Grade 4 (start symptomatic treatment when possible)		
1st Appearance	Interrupt until resolved (Grade 0–1).	Reduce by 200 mg.
2nd Appearance	Discontinue permanently.	NA
Related Grade 3 Rash (start symptomatic treatment when possible)		
1st Appearance	Interrupt until resolved (Grade 0–1).	As agreed upon by the investigator and medical monitor: Rechallenge at 200 mg/day; if safely tolerated after 1 cycle (6 weeks), dose can be re-escalated by 200mg increments to the RP2D as agreed upon by the investigator and medical monitor
2nd Appearance	Discontinue permanently.	NA
Prolonged QTcF		
QTcF >500 msec on at least 2 separate ECGs (i.e., Grade 3).	Hold PLX3397 until recovery to QTcF ≤500 msec.	Upon recovery to QTcF ≤500 msec (Grade ≤2), restart at a reduced dose (minimum reduction decrement of 200 mg). Monitor ECG and electrolytes, including potassium, magnesium, and calcium, after dose modification of PLX3397 for QTcF prolongation.
QTcF interval remains >500 msec and increased >60 msec from pretreatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias).	Permanently discontinue PLX3397.	NA

ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; INR = international normalized ratio; NA = not applicable; PLT = platelet(s); QTcF = QT interval corrected using Fridericia's formula; T = temperature = ULN = upper limit of normal

[a] Throughout the study, dose decrements of 200 mg/day of PLX3397 are permitted for management of toxicity.

Dose interruptions for toxicities that last up to 1 week but not shown on Table 3 can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. No dose reduction is required when resuming treatment.

Liver enzyme abnormalities, including increased transaminase values, have occurred with PLX3397 and should be managed as described in Table 4 and Table 5.

Table 4. Dose Modification Guidelines for Liver Function Abnormalities

Toxicity Grade CTCAE v0.4	Initial Action	Outcome	Action
ALT or AST Grade 2 (> 3-5 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor weekly Check for changes to medications and for symptoms	Resolution to Grade 0–1 or baseline (no bilirubin increase)	Restart on resolution Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Grade 3 ALT or AST increase (> 5-20 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor 2x/week[b] Check for changes to medications and for symptoms	Resolution to Grade 0–1 or baseline (no bilirubin increase) within 14 days	Restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
		ALT and AST not decreasing within 14 days of holding study drug	Proceed to liver evaluation as outlined in Table 5. Restart only on resolution to Grade 0-1/baseline at 1 dose lower (reduce by one 200 mg capsule); For max AST or ALT > 8 × ULN, consult with medical monitor prior to re-start
Grade 4 ALT or AST (> 20 × ULN)	Discontinue treatment Monitor 2x/week until resolution to Grade 2 Follow-up until resolution Grade 0-1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined in Table 5. If clear confirmed alternate cause, restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Any grade ALT or AST increase[a] with any bilirubin increase or signs of hypersensitivity	Discontinue treatment Monitor 2x/week until resolution to Grade 2 Follow-up until resolution Grade 0-1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined in Table 5. If clear confirmed alternate cause, restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

a. An increase in bilirubin is defined as all of the following: total bilirubin > ULN, total bilirubin > 20% above baseline, and direct bilirubin is > ULN. If all of these conditions are met, then bilirubin is considered increased and should be immediately re-checked. Pexidartinib treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.

b. If ALT, AST, or bilirubin worsens during the monitoring period, follow the applicable guidance for the worst toxicity grade.

Table 5. Additional Liver Evaluation

Evaluation	Comments
Increase frequency of testing liver chemistries to twice per week, including INR, and continue until liver chemistries have stabilized, and then reduce to weekly until liver chemistries return to normal or baseline.	Investigational treatment may be started after liver function tests recover to Grade 0 to 1 or baseline level, and in consultation with Medical Monitor.
Detailed history focusing on medications and substances used: alcohol, change in medication dosages, new medications added, attention to use of acetaminophen, OTC medication use, and recreational drug use. Check for change in diet or use of dietary supplements, with particular attention to dose and duration of any herbal product.	Suspect medications will be discontinued or substituted for if possible.
Detailed medical history and physical examination seeking new abnormalities.	Evaluate abnormalities found.
Full serological evaluation for hepatitis A, B, C, and E (IgG and IgM). Check for autoimmune hepatitis with serological laboratory studies.	If viral hepatitis or autoimmune hepatitis suggested, have patient evaluated by hepatologist.
Liver ultrasound performed to evaluate liver and biliary tree.	Evaluate any abnormalities found.
Check history for exposure to chemical agents.	Remove chemical exposure and have patient seen by hepatologist.
Obtain hepatology consult if liver function continues to rise beyond 14 days.	Contact Medical Monitor.
We request that cases be discussed with the Medical Monitor as defined in the protocol whenever investigational product is being held for liver function test abnormality.	

Ig = Immunoglobulin; INR = international normalized ratio; OTC = over-the-counter.

For suspected cases of cholestatic liver injury (e.g., aminotransferase increase concurrent with hyperbilirubinemia, or liver biopsy suggesting cholestasis and/or ductopenia), patients will be followed to assess long-term outcome. Additional diagnostic and follow-up procedures might be implemented as appropriate to fully assess the event.

Generally, rechallenge of subjects with significant AST/ALT elevations (>5 × ULN, Grade 3) should not be attempted. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available and the AST, ALT, or bilirubin elevations of Grade 2 or higher are deemed not related to pembrolizumab; relationship to pembrolizumab will be determined as related if 1) evidence of immune hepatitis if a liver biopsy is performed OR 2) if the Investigator otherwise assesses the AST/ALT elevations as related to pembrolizumab. Rechallenge must be discussed with the medical monitor prior to re-starting. The subject should be made aware of the potential risk and consent to the rechallenge, and the Institutional Review Board (IRB) informed. The rechallenge should start at 200 mg/day PLX3397 and, if safely tolerated after 1 cycle (6 weeks), can be re-escalated by 200mg increments to the RP2D as agreed upon by the investigator and medical monitor.

If there is Grade 2 or higher ALT or AST elevation (i.e., >3 × ULN) at any time during treatment, the subject should be followed closely, which includes:

- Obtain liver effect biomarkers: mir122, cytokeratin (18 full-length and caspase-cleaved), HMGB1 (native and acetylated). Frequency of collection as determined by the Investigator and Medical Monitor and should include a sample at 5to 8 days after PLX3397 dose hold or discontinuation.
- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Medical Monitor should be notified within 48 hours.

And may include the following:

- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Consideration of gastroenterology or hepatology consultations.

3.1.9.2. Potential Pembrolizumab Toxicities and Dose Modifications (Escalation/Titration/Other)

AEs (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6. See Section 3.1.9.2.1 for supportive care guidelines, including use of corticosteroids.

Table 6. Dose Modification Guidelines for Adverse Events Related to Pembrolizumab

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken to Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up Instructions
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST/ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5–1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable.
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[1]	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken to Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up Instructions
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue[2]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[2]		
Hypothyroidism	Grade 2–4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1–2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and are not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

General Instructions:

Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

[1] For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to Grade ≤2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

[2] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

3.1.9.2.1. Rescue Medications & Supportive Care for Reactions Associated with Administration of Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Table 6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 6 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Table 7. Treatment Guidelines for Infusion Reactions Associated with Pembrolizumab

NCI CTCAE Grade	Treatment[a]	Premedication at Subsequent Dosing
Grade 1		
Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator.	None.
Grade 2		
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite**	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500–1000 mg PO (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment[a]	Premedication at Subsequent Dosing
	adequate premedication should be permanently discontinued from further trial treatment administration.	
Grades 3 or 4		
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing.

IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = oral
[a] Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

3.1.10. Radiologic Disease Progression: Assessment and Treatment During Dose-escalation and Expansion Phases

3.1.10.1. Assessment of Radiologic Disease Progression

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such as approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

irRECIST guidelines (see the irRECIST Tip Sheet, provided in the Study Reference Manual) will be applied by the site as the primary measure for assessment of tumor response and as a basis for protocol guidelines related to disease status (e.g., discontinuation of study therapy). These guidelines will also be applied by the site to

account for the unique tumor response seen with treatment of the combination of pembrolizumab and PLX3397.

In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions. All scans will be archived. Please refer to Study Reference Manual.

Imaging during the follow-up period is to be repeated as clinically indicated for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new anti-neoplastic therapy.

3.1.10.2. Procedure and Treatment After Initial Evidence of Radiologic Disease Progression

If radiologic imaging shows PD, tumor assessment should be repeated ≥4 weeks later to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared with the initial scan demonstrating PD, treatment may be continued per the treatment calendar. If repeat imaging confirms PD, subjects will be discontinued from the study.

When feasible, subjects should not be discontinued until PD is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject (Table 8). Subjects may receive study treatment while awaiting confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation.

The Sponsor will receive radiologic images for possible retrospective analysis of subject eligibility and treatment response, to be performed by a central vendor, if an efficacy endpoint is met.

If a subject with confirmed radiologic progression is clinically stable or clinically improved and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment after consultation with the Sponsor. For clinically stable subjects to continue study treatment, the confirmatory scan should show no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) (Table 8).

Table 8. Imaging and Treatment After First Radiologic Evidence of Disease Progression

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECISTv1.1	Repeat imaging at ≥4 weeks at site to confirm PD.	May continue study treatment at the local site's Investigator discretion while awaiting confirmatory imaging by site by irRECIST.	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment.
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required.	NA
Repeat imaging shows SD, PR, or CR by irRECIST at the local site	Continue regularly scheduled imaging assessment every 9 weeks.	Continue study treatment at site's Investigator discretion.	Continue regularly scheduled imaging assessments every 9 weeks.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the every 9 week (± 7 days) imaging schedule

CR = complete response; PD = progressive disease or disease progression; PR = partial response; SD = stable disease

3.2. Selection of Doses

3.2.1. PLX3397

The dose-escalation plan, summarized in Table 1, was selected on the basis of data from Study PLX108-01, an ongoing phase 1, open-label, 2-part study of single-agent PLX3397 in subjects with advanced, incurable, solid tumors (Dose-escalation Phase) and in subjects with selected tumors (Expansion Phase). The initial Dose-escalation Phase of the trial studied total daily oral doses from 200 mg through 1200 mg. Two subjects receiving 1200 mg/day, administered as a split dose, experienced DLT toxicities: anemia, neutropenia, and syncope in 1 subject and elevated AST in the other. Thus, a RP2D of 1000 mg/day as a split dose was administered in the Extension Phase of this single-agent study. An interim analysis from the extension cohort with the longest duration of treatment (median duration of 219 days, n = 17 subjects) showed that approximately half of the subjects required a dose reduction to at least 800 mg/day as a split dose within the first 2 cycles (Plexxikon, data on file). Biomarker data have suggested that doses at or

below 400 mg/day are less likely to have pharmacodynamic activity. Thus, in consideration of data from single-agent PLX3397, 600 mg/day as a split dose is selected as the initial dose with an allowance for de-escalation to 400 mg/day as a split dose for this combination study.

Note that per Section 3.1.7.2, allowance is made for alternative dosing regimens such as intermittent dosing (e.g., 1 week off and 2 weeks on for PLX3397 during the 3-week pembrolizumab dosing interval; see Figure 1 Cohort [int] as an example and Appendix 17.7); and/or for repeating a dose level with a run-in period of PLX3397 for 2 weeks prior to starting pembrolizumab (see Appendix 17.8. Intermittent PLX3397 dosing may allow pembrolizumab to function alone for one week before initiation of PLX3397 dosing. PLX3397 could then target emergent immune suppressive macrophages in the tumor microenvironment that results from pembrolizumab activity (Tumeh 2014). The intermittent PLX3397 dosing may also provide increased safety and tolerability by avoiding simultaneous peak exposures of pembrolizumab and PLX3397. The alternative regimen of a run-in period of PLX3397 for 2 weeks is supported by empirical observations of reduced liver transaminase elevations with a combination of targeted therapy (vemurafenib) and anti-PDL1 (Hamid 2015).

3.2.2. Rationale for Pembrolizumab Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg every 3 weeks (Q3W). The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

In KEYNOTE-001, an open-label Phase 1 study conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other subject covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

3.2.3. Missed or Vomited Doses

Subjects who miss a dose of PLX3397 should be instructed NOT to make up that dose. Doses that are vomited should not be replaced.

4. STUDY POPULATION

4.1. Enrollment

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex) date and outcome of screening process (e.g., enrolled in the study, reason for ineligibility, refused to participate).

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study, allows the Investigator to reveal the identity of any subject when necessary.

All subjects must personally sign and date (unless incapable of doing so; see Section 14.2) the ICF provided by the site before pre-screening or screening procedures are performed. For additional information on Informed Consent, see Section 14.2.

4.1.1. Inclusion Criteria

A subject must satisfy all of the following criteria to be considered for inclusion in the study:

1. Be willing and able to provide written informed consent for the trial.
2. Male or female ≥18 years old.
3. Subjects with histologically or cytologically-confirmed diagnosis of cancer that is recurrent, metastatic, or persistent, who have relapsed from or are refractory to treatment and who also meet the following corresponding requirements for the cohort or phase of the study into which they will enroll:

- Dose-escalation Phase: Subjects with advanced solid tumors (any tumor type) considered to have no standard-of-care treatment for their malignancy with a curative intent, either as initial therapy or after progressing to prior therapies; subjects who have been treated previously with a CSF1R inhibitor or an anti-PD1/PDL1 inhibitor may enroll.
- Expansion Phase: Subjects with 1 of the tumor types described in Table 2, who have relapsed from or are refractory to standard treatment. Subjects with:
    i. NSCLC (non-squamous; EGFR and ALK wild-type) and SCCHN cancer must show primary progression (i.e., no PR or CR) with anti-PD1/anti-PDL1 therapy
    ii. Melanoma subgroups are as follows: (a) anti-PD-1/PD-L1 naïve and CSF1R naïve; (b) at least 4 months of prior anti-PD-1 PD-L1 therapy but never responded (i.e., no PR or CR); (c) prior anti-PD-1/PD-L1 therapy and responded but later progressed as defined by irRECIST while on therapy
    iii. Ovarian includes primary peritoneal and fallopian tube cancers; (carcinosarcomas and low grade serous tumors are excluded)
    iv. Unresectable RCC with component of clear-cell histology and/or component of sarcomatoid histology
    v. World Health Organization Grade IV supratentorial malignant glioma (glioblastoma or gliosarcoma) following complete or partial surgical resection and radiation plus temozolomide
    vi. GIST cohort must have locally advanced or metastatic disease and have progressed on or have been intolerant to imatinib therapy.
    vii. All tumor types must be naïve to anti PD1/PDL1 inhibitors except as described in (i) and (ii).

4. Subjects with melanoma must have a histologically confirmed diagnosis of stage III or stage IV disease not amenable to local therapy. Melanoma subjects may have received any number of prior lines of therapy for metastatic disease and must have measurable disease per RECISTv1.1 (Appendix 17.4). Cutaneous lesions and other superficial lesions that are detectable only by physical examination are not considered measurable lesions for the purposes of this protocol, but may be considered as nontarget lesions. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Subjects with melanoma who have received prior treatment with a MEK/BRAF inhibitor are acceptable candidates.
5. Expansion cohorts: Subjects must have relapsed or been refractory to standard treatment and have measurable disease per RECISTv1.1, using MRI or CT, with FDG-PET for GIST subjects only. They must have tumor accessible for sequential biopsy (core needle biopsy or excision required) and be willing to provide on-study tumor tissue biopsy. Repeat samples may be required if adequate tissue is not provided. When possible, newly obtained tissue should be collected from a non-target lesion. Subjects for whom newly obtained samples cannot be obtained (e.g. inaccessible or patient safety concern, glioblastoma tumor type) may submit an archived specimen only upon agreement from the Sponsor.
6. ECOG performance status 0 or 1 (Appendix 17.3).
7. Women of childbearing potential must have a negative serum pregnancy test within 72 hours prior to initiation of dosing.
8. Women of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Effective forms of contraception include abstinence, hormonal contraceptive in conjunction with a barrier method, or a double-barrier method. Women of nonchildbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year.
9. Fertile men must agree to use an effective method of birth control starting with the first dose of study treatment through 120 days after the last dose of study treatment.
10. Adequate organ function as demonstrated by the laboratory values shown below. These laboratory tests should be performed within 10 days prior to the first dose of study treatment.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine OR Measured or calculated[a] creatinine clearance (crcl) (GFR can also be used in place of creatinine or crcl)	≤1.5 × ULN OR ≥60 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.25 × ULN (Gilbert's Syndrome allowed)
AST and ALT	≤1.5 × ULN
Coagulation	
INR or PT	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
aPTT	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

aPTT = activated partial thromboplastin time; ALT = alanine aminotransferase;
ANC = absolute neutrophil count; AST = aspartate aminotransferase;
INR = international normalized ratio; PT = Prothrombin time;
ULN = upper limit of normal

[a] Creatinine clearance should be calculated per institutional standard.

4.1.2. Exclusion Criteria

A subject who meets any of the following criteria will be disqualified from entering the study:

1. Disease that is suitable for local therapy administered with curative intent.
2. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
3. 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 the first dose of study treatment.
4. Has had monoclonal antibody treatment for cancer within 28 days of first dose of study treatment or has not recovered from AEs due to agents administered more than 28 days earlier (i.e., AEs should be ≤Grade 1 or ≤the value collected at baseline).
5. Has had chemotherapy, targeted small molecule therapy, or radiation therapy >30 Gray within 14 days prior to first dose of study treatment or

who has not recovered (i.e., AEs should be ≤Grade 1 or ≤the value collected at baseline) from AEs due to a previously administered intervention.

Note: Subjects with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.

6. Has received transfusion of blood products (including platelets or red blood cells [RBC]) or administration of colony stimulating factors (including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or recombinant erythropoietin) within 28 days prior to Day 1.
7. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer and isolated elevation of prostate-specific antigen. Subjects with a completely treated prior malignancy with no evidence of disease for ≥2 years are eligible.
9. For Dose-escalation Cohort [-1]: Patients with liver metastases; inclusion of patients with liver metastases in subsequent cohorts will be based upon clinical safety data.
10. For Expansion cohort subjects who have previously received an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or has previously participated in pembrolizumab clinical trials are excluded, except those tumor types listed under Inclusion Criteria #3.
11. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
12. Has an active infection requiring systemic therapy.
13. Has known central nervous system metastases and/or carcinomatous meningitis.
    Note: Subjects with previously treated brain metastases may participate if they meet the following criteria: 1) are stable (i.e., no evidence of progression per irRECIST (see the irRECIST Tip Sheet, provided in the Study Reference Manual) determined by imaging, using the identical imaging modality for each assessment, either MRI or CT scan) for at least 35 days prior to the first dose of study treatment and if all neurologic symptoms returned to baseline; 2) have no evidence of new or enlarging brain metastases; and 3) have not been using steroids for at least 7 days prior

to first dose of study treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

14. Uncontrolled intercurrent illness.
15. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate absorption.
16. QT interval corrected using Fridericia's formula (QTc) ≥450 msec (males) or ≥470 msec (females) at Screening.
17. Congenital long QT syndrome or patients taking concomitant medications known to prolong the QT interval. A list of drugs known to prolong the QT interval can be found in Appendix 17.1.
18. Major surgery within 28 days prior to first dose of study treatment.

    Note: If subject received major surgery, he or she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
19. History of active ethanol abuse.
20. Has received a live vaccine administered within 30 days of planned treatment start or while participating in the trial. Seasonal flu vaccines that do not contain live virus are permitted.
21. 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.
22. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies); has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
23. Any of the following within 48 weeks (~1 year) prior to first dose of study treatment: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.
24. Imprisoned or under legal guardianship.
25. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of study treatment.
26. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
27. Has had prior exposure to PLX3397.
28. Has had hypersensitivity (≥Grade 3) reaction to pembrolizumab and/or any of its excipients.

4.2. Removal of Subjects From Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

- Screen failure
- AE
- Withdrawal by subject
- Physician's Decision

Subjects maybe discontinued from treatment during the treatment phase of the trial (i.e., during the Dose-escalation and/or Expansion Phase of the study), in cases of:

- Unacceptable or intolerable AE
- Lost to Follow-up
- Withdrawal of consent by subject
- Physician's decision
- Death
- Lack of efficacy
- Pregnancy
- Progressive disease by irRECIST (see the irRECIST Tip Sheet, provided in the Study Reference Manual)
- Study terminated by Sponsor
- Other reasons

4.2.2. Withdrawal Procedures

If a subject withdraws from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified end-of-treatment procedures (Section 6.5).

4.2.3. Subject Replacement

If treatment interruptions meet either of the following criteria for reasons other than a DLT, the subject can be replaced: (1) for more than 10 days (11 days or more) during the 42-day DLT observation period (within 6 weeks of C1D1) or (2) for more than 7 days (8 days or more) during the run-in period of 2 weeks of PLX3397.

If a subject discontinues treatment during the Expansion Phase of the study, that subject will not be replaced.

4.2.4. Subject Rescreening Procedures

Subjects can be rescreened if they were deemed a screen failure (i.e., met ≥1 exclusion criteria as specified in Section 4.1.2) due to ineligible laboratory values that recovered without medical intervention. However, screening procedures must be restarted within 28 days from the screen failure (or the communication of the results to the site, in case of screen failures related to the tissue sample).

The Principal Investigator will consult with the Sponsors or the contract research organization (CRO) before making the re-screen decision.

Re-screened subjects will keep the same identification number they were assigned at first screening.

4.2.5. Discontinuation of Study Treatment after Complete Response

Discontinuation of both Study Drugs may be considered for subjects who have attained a confirmed CR and who have been treated for at least 24 weeks (4 cycles) with pembrolizumab and PLX3397 and had at least 2 treatments with pembrolizumab (and PLX3397) beyond the date when the initial CR was declared.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

For combination treatment, there are 2 investigational products, pembrolizumab and PLX3397, described in the sections that follow. The Investigator must ensure that the investigational products described below will be used only in accordance with the protocol.

5.1.1. Pembrolizumab

Pembrolizumab was approved in the US on September 2014 as a single agent for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab, and if BRAF V600 mutative positive, a BRAF inhibitor. Pembrolizumab (Table 9) will be supplied by Plexxikon to the study sites. During both the Dose-escalation and Expansion Phases of the study, subjects will receive pembrolizumab 200 mg IV over 30 minutes once every 3 weeks. Instructions for preparation and administration of pembrolizumab are provided in Section 5.4.1.1.

5.1.2. PLX3397

PLX3397 is formulated as an HCl salt capsule (200-mg strength of the active free base of PLX3397). PLX3397 HCl Salt will be referred to as PLX3397 throughout this document. During the Dose-escalation Phase of the study, up to 42 subjects in up to 7 cohorts will receive PLX3397 as summarized in Table 1. During the Expansion Phase, subjects with

1 of the tumor types (Table 2) will receive PLX3397 at the RP2D (Table 2). Instructions for preparation and administration of PLX3397 are provided in Section 5.4.1.2.

5.2. Method of Assigning Subjects to Treatments

Once all screening procedures have been completed and study eligibility has been confirmed, a subject will be considered enrolled in the study. Eligible subjects who enter the Dose-escalation Phase of the study will be assigned sequentially to 1 of the cohorts and receive treatment as described in Table 1 (a fourth cohort, 400 mg/day of PLX3397 is an option if subjects do not tolerate PLX3397 at 600 mg/day). After completion of the Dose-escalation Phase, subjects may continue to receive treatment with pembrolizumab 200 mg IV every 3 weeks at the dose of PLX3397 determined for their cohort or may have the dose of PLX3397 changed to the RP2D, if warranted in the judgment of the Investigator.

Eligible subjects who enter directly into the Expansion Phase of the study (i.e., did not participate in the Dose-escalation Phase) will have 1 of the tumor types described in Table 2 and will receive pembrolizumab 200 mg IV every 3 weeks in combination with the RP2D of PLX3397.

5.3. Method of Assessing Treatment Compliance

At the study visits indicated in the Schedule of Events (Appendix 17.6), unblinded PLX3397 will be dispensed to subjects. The appropriate study personnel will document and maintain records of PLX3397 dispensed to each subject and return of any amount of PLX3397 at each study visit. Subjects will complete a dosing Diary to record the number of capsules/date/time taken during each dosing cycle. At each clinic visit, subjects will be assessed for compliance with study treatment administration.

Compliance with treatment with pembrolizumab is assured by having study personnel administer the drug IV at 200 mg over 30 minutes every 3 weeks at the time points indicated in the Schedule of Events (Appendix 17.6).

Further details regarding treatment compliance can be found in the Plexxikon Study Reference Manual.

5.4. Labeling and Packaging

PLX3397 HCl capsules (200-mg strength of the active free base of PLX3397) are manufactured, packaged, and labeled according to Good Manufacturing Practices (GMP) and Good Clinical Practices (GCP).

PLX3397 HCl capsules will be provided to the study sites by Plexxikon.

Pembrolizumab (Table 9) will be provided to the study sites by Plexxikon.

Table 9. Pembrolizumab Product Description

Product Name and Potency	Dosage Form
MK-3475 50 mg	Lyophilized Powder for Injection
MK-3475 100 mg/4mL	Solution for Injection

5.4.1. Preparation and Administration

5.4.1.1. Pembrolizumab

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 3.1.8). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 [-5/+10] minutes).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

5.4.1.2. PLX3397

No preparation is required for PLX3397. PLX3397 capsules will be administered orally twice daily as a split dose on an outpatient basis, except as indicated in the Schedule of Events (Appendix 17.6), when subjects will bring their morning dose to the clinic and receive it under the supervision of the study site staff. For patients who receive their medications through PEG tubes, e.g., those with tumors of the head and neck, PLX3397 may be administered through the PEG tube. Study Drug preparation and method of delivery should remain the same for the duration of study. Preparation and administration of PLX3397 can be found in the Pharmacy Manual.

Administration of PLX3397 will begin at C1D1 visit in the morning, at which time subjects will also receive their first 30-minute IV infusion of pembrolizumab 200 mg/day. At that visit, subjects in Cohort 1 (600 mg/day) will receive 3 capsules of PLX3397 at 200 mg per capsule. Subjects will be instructed to take 1 capsule in the morning (i.e., 200 mg PLX3397) and 2 capsules (i.e., 400 mg of PLX3397) in the evening. Subjects in Cohort 2 (800 mg/day) will receive 4 capsules of PLX3397. They will be instructed to take 2 capsules in the morning (i.e., 400 mg PLX3397) and 2 capsules in the evening (i.e., 400 mg PLX3397). Subjects at the 1000 mg/day PLX3397 dose level will be instructed to take 2 capsules (i.e., 400 mg PLX3397) in the morning and 3 capsules (i.e., 600 mg PLX3397) in the evening.

Alternative PLX3397 dose regimens may be employed to optimize safety in combination with pembrolizumab (see Section 3.1.7.2, Appendix 17.7, and Appendix 17.8). The intermediate dose level or regimen will be determined by the Sponsor and Investigators.

PLX3397 should be taken with 240 mL (8 oz.) of water while in the fasting state (i.e., no food for 1 hour before and 2 hours after dose administration). However, during the fasting period, subjects will be permitted to eat a low-fat snack (e.g., crackers, toast, tea), if necessary. Doses will be taken at approximately the same times of the day, approximately 12 hours apart, with the exception of PK draw days, where the second dose of the day may be less than 12 hours from prior dose.

5.4.2. Storage and Stability

PLX3397 HCl capsules will be stored at the clinical site, as indicated on the Study Drug label, i.e., room temperature (do not store above 25ºC/77ºF). Excursions are permitted from 15ºC to 30ºC (59ºF to 86ºF).

Subjects will be requested to store the PLX3397 at the recommended storage conditions noted on the label, out of the reach of children or other cohabitants.

Pembrolizumab vials must be stored under refrigeration at 2°C to 8°C (36°F to 46°F). See Section 16 of the Keytruda Package Insert.

5.4.3. Investigator and Site Responsibility for Drug Accountability

Accountability for the Study Drug at the trial site is the responsibility of the Investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and amount returned to Plexxikon, or a CRO designee, (or disposal of the drug, if approved by Plexxikon) will be maintained by the clinical site. Plexxikon or its CRO designee will review drug accountability at the site on an ongoing basis.

All material containing Study Drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

5.4.4. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Plexxikon quality representative.

For Product Complaints, refer to the Study Pharmacy Manual for instructions and details.

5.5. Concomitant Medications and Therapies

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the Study Drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an AE), the treatment must be recorded on the CRF, including the reason for treatment, generic name of the drug, dosage, route, and date and time of administration.

All concomitant medications received within 30 days before the first dose of trial treatment and 28 days after the last dose of trial treatment should be recorded Concomitant medications received greater than 30 days before the first dose of trial treatment may be recorded if deemed relevant to adverse events and/or clinically important medical history. Concomitant medications administered after 28 days after the last dose of trial treatment should be recorded for SAEs and ECI as specified in Section 11.2 and Section 11.6, respectively.

5.5.1. Concomitant Medications and Therapies Related to PLX3397

Although PLX3397 does not appear to inhibit cytochrome P450 (CYP) drug-metabolizing enzymes to an important extent, caution is warranted when administering PLX3397 to subjects taking drugs that are highly dependent on cytochrome P450 3A4 (CYP3A4) for metabolism and have a narrow therapeutic index. It is not known whether systemic exposure to these medications will demonstrate an increase while subjects are receiving PLX3397.

Of the 5 major CYP isoforms, 3A4 may be involved in Phase 1 metabolism of PLX3397, with possibly cytochrome P450 1A2 (CYP1A2) playing a minor role. Until information regarding exposure-toxicity and exposure-response relationships are available with PLX3397, concomitant CYP3A4 inhibitors and inducers should be administered with caution, in the event they alter the systemic exposure to PLX3397 (see Appendix 17.2 for a list of common CYP3A4 inhibitors and inducers). In general, strong inhibitors or inducers of CYP3A4 should be avoided unless clinically necessary. These include anticonvulsants, mycin antimicrobials, and antiretrovirals.

Subjects are discouraged from taking proton pump inhibitors (PPIs) or other strong anti-acids (e.g., H-2 antagonists), as these may interfere with the reliable identification of the MTD or R2PD for PLX3397 when used in combination with a fixed dose of pembrolizumab.

5.5.2. Concomitant Medications/Vaccinations Related to Pembrolizumab (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the Sponsor's medical monitor. The final decision regarding any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor and the subject.

5.5.2.1. Acceptable Concomitant Medications with Pembrolizumab

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. All concomitant medication will be recorded on 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.

5.5.2.2. Prohibited Concomitant Medications with Pembrolizumab

Subjects are prohibited from receiving the following therapies during the Screening and Treatment periods (including retreatment for post-CR relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and PLX3397
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with Sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative RT will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: Inhaled (nasal or pulmonary), ophthalmic, topical steroids and local steroid injection are allowed.

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Subjects may receive other medications that the Investigator deems to be medically necessary.

Also see Section 4.1.2, Exclusion Criteria, which describes other medications that are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up period of the study (the Schedule of Events is provided in Appendix 17.6).

6. STUDY PROCEDURES FOR THE DOSE-ESCALATION AND EXPANSION PHASES

A Schedule of Events for the Dose-escalation and Expansion Phases is provided in Appendix 17.6, Appendix 17.7 (intermittent PLX3397 alternate dosing regimen), and Appendix 17.8 (run-in PLX3397 alternate dosing regimen). After written informed consent is obtained, a subject's eligibility for the study and baseline disease status will be assessed. A subject must sign the consent form prior to starting any study-related procedures or assessments.

The procedures below follow the Schedule of Events in Appendix 17.6, unless otherwise indicated.

6.1. Screening (Day -28 to Day -1)

The following activities and/or assessments will be performed at/during Screening:

- Informed consent, if not already obtained
- Determination of eligibility.
- Medical history.
- Concomitant medication review.
- Full physical examination, including height, weight, and vital signs (blood pressure, respiratory rate, pulse rate, and body temperature [°F]).
- ECOG performance status.
- AE assessment.
- ECG.
- Tumor imaging [CT, MRI, FDG-PET (for GIST subjects only)].
- Digital photography: cutaneous lesions.
- Tumor Tissue Collection (optional for Dose-escalation, required for Phase 2 Expansion, unless deemed medically unsafe by the Investigator)
- Blood sample collection for complete blood count (CBC) with differential; comprehensive serum chemistry; liver function tests; serum pregnancy test (women of childbearing potential only); HBV surface antigen test; HCV antibody test; coagulation studies (prothrombin time [PT]; activated partial thromboplastin time [aPTT], INR) (Appendix 17.5).
- Urine sample collection for urinalysis with microscopic exam.

6.2. Randomization

Not applicable. This is an open-label study.

6.3. Run-in Period

A run-in dosing period with PLX3397 (see Appendix 17.8) may be implemented as an alternative dosing regimen. After screening, PLX3397 would be administered for 2 weeks prior to C1D1 (i.e., first dose of pembrolizumab).

6.4. Treatment Period

Cycle 1 Day 1 is defined as the day of first pembrolizumab administration. For intermittent dosing with PLX3397 see Appendix 17.7 and Run-in, Appendix 17.8.

6.4.1. Cycle 1 (-2 days for assessments on Day 1; ± 3 days for assessments other than Day 1)

- Concomitant medication review: Days 1, 8, 15, 22, 29, 36.
- Directed physical examination: Days 1, 8, 15, 22 or as clinically indicated.

- Assessment of Study Drug compliance: Days 8, 15, 22, 29, 36.
- ECOG performance status assessment: Day 1.
- Vital signs, including height (Day 1 only) and weight: Days 1, 8, 15, 22, 29, 36.
- AE monitoring: Days 1, 8, 15, 22, 29, 36.
- Blood sample collection for complete blood count (CBC) with differential: Days 1, 8, 15, 22, 29, 36.
- Blood sample collection for comprehensive serum chemistry panel: Days 1, 8, 15, 22, 29, 36.
- Blood sample collection for liver function tests: Days 1, 8, 15, 22, 29, 36.
- Blood sample collection for exploratory biomarkers of drug effects on liver: Days 1 (predose), 8, 15, 22, 29.
- Blood sample collection for MDSC: Days 1 (predose), 15
- Blood sample collection for thyroid function tests: Day 1.
- Urine sample collection for urinalysis with microscopic exam: Days 1 and 22.
- Pregnancy test (serum beta human chorionic gonadotropin [β-hCG]) for women of childbearing potential only: must be performed ≤72 hours before dosing on Day 1.
- Electrocardiogram (ECG): Days 1 and 15.
- Administration of IV pembrolizumab: Days 1 and 22.
- Administration of oral PLX3397: Each day of Cycle 1 (i.e., Days 1 through 42). (for Cohort [int], Days 8 through 21, then 29 through 42)
- Blood sample collection for PK and anti-pembrolizumab antibodies: see Table 10 for continuous dosing, Appendix 17.7 for intermittent dosing.
- Tumor tissue collection: Optional for Dose-escalation, required for Phase 2 Expansion, unless deemed medically unsafe by the Investigator. Day 29 for continuous PLX3397 regimen (Day 22 for intermittent dosing). (For days other than Day 1, If PLX3397 study drug interruption occurs during the week prior to the on-treatment biopsy, the Medical Monitor should be contacted.)
- Exploratory pharmacology blood sample collection: predose on Days 1, 22 and 29

6.4.2. Cycle 2 (± 3 days)

- Concomitant medication review: Days 1, 8, 15, and 22.
- Assessment of Study Drug compliance: Days 1 and 22.

- Physical examination
  - Full physical examination, weight, and vital signs (blood pressure, respiratory rate, pulse rate, and body temperature [°F]): Day 1.
  - At other visits, directed physical examination: As clinically indicated.
- ECOG performance status assessment: Day 1.
- Vital signs, including weight: Days 1 and 22.
- Tumor imaging [CT, MRI, FDG-PET (for GIST subjects only)].
- AE monitoring: Days 1 and 22.
- Blood sample collection for CBC with differential: Day 1 and 22.
- Urine sample collection for urinalysis with microscopic examination: Day 1.
- Blood sample collection for comprehensive serum chemistry panel: Days 1 and 22.
- Blood sample collection for liver function tests: Days 1, 8, 15 and 22.
- Blood sample collection for thyroid function tests: Day 1.
- ECG: Day 1
- Administration of IV pembrolizumab: Days 1 and 22.
- Administration of oral PLX3397: Each day of Cycle 2 (i.e., Days 1 through 42). (Cohort [int], Days 8 through 21, then 29 through 42)
- Blood sample collection for PK and anti-pembrolizumab antibodies: Day 1 (see Table 10).

6.4.3. Cycle 3 (± 3 days)

- Concomitant medication review: Days 1 and 22.
- Assessment of Study Drug compliance: Days 1 and 22.
- Physical examination
  - Full physical examination, weight, and vital signs (blood pressure, respiratory rate, pulse rate, and body temperature [°F]): Day 1.
  - At other visits, directed physical examination: As clinically indicated.
- ECOG performance status assessment: Day 1.
- Vital signs, including weight: Days 1 and 22.
- AE monitoring: Days 1 and 22.
- Blood sample collection for CBC with differential: Day 1 and Day 22.
- Blood sample collection for thyroid function tests: Day 1.
- Urine sample collection for urinalysis with microscopic examination: Day 1.

- Blood sample collection for comprehensive serum chemistry panel: Day 1 and Day 22.
- Blood sample collection for liver function tests: Day 1 and Day 22.
- ECG: Day 1.
- Administration of IV pembrolizumab: Days 1 and 22.
- Administration of oral PLX3397: Each day of Cycle 3 (i.e., Days 1 through 42). (Cohort [int], Days 8 through 21, then 29 through 42)
- Blood sample collection for PLX3397 PK: Day 1 (see Table 10)

6.4.4. Cycle 4 and Beyond (± 3 days)

- Concomitant medication review: Days 1 and 22.
- Assessment of Study Drug compliance: Days 1 and 22.
- Physical examination
  - Full physical examination, weight, and vital signs (blood pressure, respiratory rate, pulse rate, and body temperature [°F]): Day 1.
  - At other visits, directed physical examination: As clinically indicated.
- ECOG performance status assessment: Day 1.
- Vital signs, including height (Day 1 only) and weight: Days 1 and 22.
- Tumor imaging [CT, MRI, FDG-PET (for GIST subjects only)].
- AE monitoring: Days 1 and 22.
- Blood sample collection for CBC with differential: Day 1 and Day 22.
- Blood sample collection for thyroid function tests: Day 1.
- Urine sample collection for urinalysis with microscopic examination: Day 1.
- Blood sample collection for comprehensive serum chemistry panel: Day 1 and Day 22.
- Blood sample collection for liver function tests: Day 1 and Day 22.
- ECG: Day 1.
- Administration of IV pembrolizumab: Days 1 and 22.
- Administration of oral PLX3397: Each day of Cycle 4 (i.e., Days 1 through 42).
- Blood sampling for PK (beginning Cycle 8 PK every other cycle) and anti-pembrolizumab antibodies (every other cycle): Day 1 (see Table 10).

6.5. End of Treatment (+3 days)

The following procedures will be performed at time of the subject's last dose:

- Concomitant medication review.
- Assessment of Study Drug compliance.
- Assessment of post-treatment discontinuation anticancer therapy status.
- AE monitoring.
- Full Physical Exam
- ECOG performance status assessment.
- Vital signs, including weight.
- Blood sample collection for CBC with differential.
- Urine sample collection for urinalysis with microscopic examination.
- Blood sample collection for comprehensive serum chemistry panel.
- Blood sample collection for liver function tests.
- Blood sample collection for exploratory biomarkers of drug effects on liver.
- ECG.
- Tumor imaging, if not completed within the previous 7 days.
- Digital photography of cutaneous lesions, if clinically indicated.
- Tumor tissue collection - optional. (If PLX3397 study drug interruption occurs during the week prior to the on-treatment biopsy, the Medical Monitor should be contacted.)
- Exploratory pharmacology blood sample collection.

6.6. Follow-up

6.6.1. Safety Follow-up (28 days ± 7 days)

The safety follow-up visit will occur 28 days (± 7 days) after completion or discontinuation from study treatment.

- Concomitant medication review.
- Assessment of post-treatment discontinuation anticancer therapy status.
- AE monitoring.
- Vital signs, including weight.
- Blood sample collection for CBC with differential.
- Urine sample collection for urinalysis with microscopic examination.
- Blood sample collection for comprehensive serum chemistry panel.
- Blood sample collection for liver function tests.
- Blood sample collection for thyroid function tests.

- Blood sample collection for pembrolizumab PK and anti-pembrolizumab antibodies: see Table 10.

6.6.2. SAE Follow-Up (± 7 days)

SAE monitoring (12-week follow-up only if the patient has not started other chemotherapy, see Section 11.2) will occur every 12 weeks (± 7 days) via telephone or from available clinic notes, after completion or discontinuation from treatment.

6.7. Follow-up

6.7.1. Safety Follow-up (28 days ± 7 days)

The safety follow-up visit will occur 28 days (± 3 days) after the subject's last dose.

- Concomitant medication review
- Assessment of post-treatment discontinuation anticancer therapy status.
- AE monitoring.
- Directed physical exam as clinically indicated. Vital signs, including weight.
- Blood sample collection for CBC with differential.
- Blood sample collection for thyroid function tests.
- Urine sample collection for urinalysis with microscopic examination.
- Blood sample collection for comprehensive serum chemistry panel.
- Blood sample collection for liver function tests.

7. PROTOCOL DEVIATIONS

The Sponsor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject who was deemed ineligible or received the incorrect dose or investigational treatment had at least 1 dose of investigational product, data should be collected for that subject for safety purposes.

The Investigator should notify the IRB of significant deviations from the protocol in accordance with local procedures.

8. EFFICACY ASSESSMENTS

8.1. Primary Efficacy Variable: Dose-escalation Phase

There is no primary variable for clinical efficacy.

8.2. Secondary Efficacy Variable: Expansion Phase

The secondary efficacy variable is ORR as determined by RECISTv1.1 guidelines (Appendix 17.4) and applies to the Expansion Phase only of the study. Objective response rate will be assessed separately for each of the tumor types.

Rationale for Determining ORR by RECISTv1.1 and by irRECIST

In addition to RECISTv1.1 guidelines, (per Eisenhauer 2009; see Appendix 17.4), irRECIST guidelines will be used to account for the unique tumor response characteristics seen with treatment of the combination of pembrolizumab and PLX3397 (see the irRECIST Tip Sheet, provided in the Study Reference Manual). Immunotherapeutic agents such as PLX3397 and pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECISTv1.1 will be used with the following adaptations:

- If radiologic imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing assigned study treatment while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued/resumed. If repeat imaging confirms PD, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (please refer to the Site Imaging Manual).
- In subjects who have initial radiological evidence of PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:
  - Absence of signs and symptoms indicating disease progression
  - No decline in ECOG performance status
  - Absence of rapid progression of disease
  - Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- When feasible, subjects should not be discontinued until progression is confirmed. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

9. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

9.1. Pharmacokinetic Variables

The PK profile of plasma PLX3397 will be analyzed by measurement of area under the plasma concentration–time curve from time zero to 6 hours (AUC_{0-6}), C_{max}, and T_{max}. Dose proportionality following study treatment will be explored by analyzing natural log-transformed pharmacokinetic variables, AUC_{0-6}, and C_{max}, with a linear model including the natural log-transformed dose as a covariate. Dose linearity for AUC_{0-6}, and C_{max} will also be explored by a linear model.

A formal PK statistical analysis plan will be created for this protocol, and a separate formal PK report will be written for inclusion in the final study report.

A formal PK analysis of pembrolizumab levels will not be carried out in view of the lack of CYP-mediated drug-drug interaction for pembrolizumab.

9.2. Pharmacodynamic Variables

PK samples scheduled in Table 10 may be used for pharmacodynamic biomarkers as indicated in the Schedule of Events (Appendix 17.6 and Appendix 17.7) and will be analyzed for immunoregulatory effects of pembrolizumab and PLX3397, e.g., CD8 immunohistochemistry. Preparation, handling and shipping of samples will be provided in the Laboratory Manual.

9.3. Biomarker and Exploratory Variables

Blood samples (plasma and serum) will be collected to measure biomarkers of drug effects on liver at the following time points: Pre-Treatment, Day 8, Day 15, Day 22, Day 29, and 5 to 8 days after PLX3397 is withheld or discontinued and for subjects who experience Grade 2 or higher elevations in AST or ALT, preferably when elevations are still present. Preparation, handling and shipping of blood samples will be provided in the Laboratory Manual.

Blood samples will be collected to assess MDSC at Cycle 1 Day 1 and Cycle 1 Day 15. Preparation, handling and shipping of blood samples will be provided in the Laboratory Manual.

Pre- and post-treatment tissue (core needle or excisional biopsy required) will be archived for RNA analyses related to effects of pembrolizumab and PLX3397 on immune cells. For example, tissue will be analyzed for PD-L1, CD8, CD68, and NanoString. Preparation, handling and shipping of samples will be provided in the Lab Manual. Subjects for whom newly obtained samples cannot be obtained (e.g., inaccessible or patient safety concern) may submit an archived specimen only upon agreement from the Sponsor.

9.4. Timing of Assessments

9.4.1. Routine Assessments

Pharmacokinetic (PK) and Pharmacodynamic assessments to be performed during the study are summarized in Table 10 and the Schedule of Events, Appendix 17.6. For intermittent dosing see Appendix 17.7. For the PLX3397 run-in, a trough PK sample will be required at the end of the run-in period, i.e., C1D1.

Table 10. Pharmacokinetic and Pharmacodynamic Assessments in Study PLX108-14: Dose-escalation and Expansion Phases

	Drug Treatment											Post-treatment
Combination Dosing Cycle	**C1D1**	**C1D4–8**	**C1D15**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**EOT**	**28 days**
Dose-escalation Phase: PK Assessments												
Pembrolizumab	X[a]	X[b]	X[c]	X[d]		X[d]		X[d]		X[d,e]		
PLX3397[f]	X		X	X	X	X	X	X	X	X		
Expansion Phase: PK Assessments												
Pembrolizumab	X[a]	X[b]	X[c]	X[d]								
PLX3397[g]			X	X								
Anti-drug Antibody Tests												
Anti-pembrolizumab antibody test[h]	X			X								

C = cycle (42 days); D = day; PK = pharmacokinetic; EOT = End of Treatment (date of last dose)

Note (1): Subjects will self-administer PLX3397 twice daily as a split dose at home. However, on days on which subjects are scheduled for clinic visits (see Appendix 17.6), subjects will bring their morning dose of PLX3397 to the clinic and receive it under the supervision of study site staff. If the patient has already taken their morning dose of PLX3397 prior to a PLX3397 trough PK day, do collect a PK sample even though it is not a trough sample.

Note (2): PK samples can be used for pharmacodynamics assays.

Note (3): PLX3397 trough PK sample will be drawn predose at -30 minutes (± 15 minutes). PLX3397 detailed PK sampling will be drawn post dose at 30 minutes (± 15 minutes), and 1, 2, 4, and 6 hours (± 30 minutes).

Note (4): For intermittent PLX3397 PK sampling see Appendix 17.7; for run in PLX3397 PK sampling see Appendix 17.8.

[a] C1D1: Collect samples predose within 24 hours of dosing of pembrolizumab and before dosing of PLX3397; post dose (within 30 minutes after end-of-infusion of pembrolizumab); and post dose 24 hours after end-of-infusion.

[b] C1D4–8: Collect a sample post dose between 72–168 hours after end-of-infusion.

[c] C1D15: Collect a sample post dose 336 hours after C1D1 end-of-infusion.

[d] C2D1, C4D1, C6D1, C8D1 and then every 2 cycles (12 weeks) thereafter: Collect samples predose within 24 hours before administration of pembrolizumab and before administration of PLX3397.

[e] C8D1: Collect samples post dose (within 30 minutes after end-of-infusion of pembrolizumab).

[f] PLX3397 PK sampling time points (Dose-escalation Phase): PLX3397 detailed PK sampling will be drawn on the first day of PLX3397 dosing (C1D1 for standard dosing Appendix 17.6; for intermittent PLX3397 PK sampling and dosing see Appendix 17.7). PLX3397 trough PK sample and detailed PK sampling will be drawn after the first 2 weeks of dosing (e.g., C1D15 for standard dosing). For subsequent cycles, PLX3397 trough PK samples will be drawn on the first day for that cycle (e.g., C2D1).

[g] PLX3397 trough PK sample and detailed PK sampling will be drawn after two weeks of dosing (C1D15 for standard dosing). If PLX3397 study drug interruption occurs during the week prior to a scheduled PK blood sampling, the Medical Monitor should be contacted. For cycle 2, PLX3397 trough PK samples will be drawn on the first day for that cycle (i.e., C2D1). No PK samples will be collected from Cycle 3 and onward. However, PK blood samples may be requested if the subject undergoes a dose adjustment or experiences an SAE or ECI. Time since the last dose of PLX3397 should be noted. If a subject undergoes a dose adjustment, a trough sample and a 2 hour postdose sample (± 30 minutes) may be requested within approximately 2 weeks.

[h] C1D1, C2D1, C4D1, C6D1, C8D1 and D1 every 2 cycles (12 weeks) thereafter: Collect samples for anti-pembrolizumab antibody test predose within 24 hours before infusion at the same time the pembrolizumab PK samples are collected.

9.4.2. Additional Pharmacokinetic Assessments

Additional post-dose peak PK samples will be drawn within 30 minutes after the end of pembrolizumab infusion at Cycles 1 and 8. An additional single PK sample should be drawn at 24 hours (Day 2), between 72 and 168 hours (Day 4–8) and 336 hours (Day 15) after Cycle 1 dosing.

10. SAFETY ASSESSMENTS

10.1. General Procedures for Assessing and Recording Adverse Events

All AEs will be recorded from the time the consent form is signed through 28 days following cessation of study treatment and at each examination. The reporting timeframe for AEs that meet any serious criteria (i.e., are SAEs) is described in Section 11.2 and for ECIs in Section 11.6.

Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to the first dose will be recorded as part of medical history (including all events occurring during the screening period). All SAEs are to be reported according to the procedures in Section 11.2 SAE Reporting-Procedure for Investigators. Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedure or treatment requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 10.1.1 for definitions, including Progression of Cancer). For deaths, the underlying or immediate cause of death should always be reported as an SAE unless due only to disease progression unrelated to Study Drug. Disease progression is a study endpoint and consequently, should not be reported as an AE/SAE (Section 10.1.1.2). In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to Study Drug should also be reported and managed as an SAE.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.1.1. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. All laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be

recorded as an AE on the CRF, and if serious, report as an SAE following the procedures in Section 11.2.

The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

10.1.1. Definitions

10.1.1.1. Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine, those circumstances or abnormal lab findings which should be considered AEs.

10.1.1.2. Progression of Cancer

Disease progression is a study endpoint and should not be reported as an AE/SAE unless it is considered to be drug-related by the Investigator.

10.1.1.3. Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization longer than 24 hours or prolongation of existing hospitalization. An emergency room visit without hospitalization is not considered a hospitalization.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Guidance for determining whether an event should be assessed as serious in nature:

- The term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, Oct 1994).

- The term *important medical event* is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate for an *important medical event.*
- A procedure (e.g., surgery, radiation) is not an AE or SAE, but the reason for the procedure may be an AE or SAE.
- Preplanned (i.e., prior to signing the ICF) procedures or treatment requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

10.1.2. Adverse Event Severity

All AEs will be graded (1 to 5; see below) according to NCI CTCAE. For AEs not listed, the following guideline should be used:

- Grade 1: Mild AE, defined as, awareness of sign or symptom; however, these are easily tolerated and, does not interfere with activities of daily living (ADL).
- Grade 2: Moderate AE, defined as discomfort enough to cause interference with ADL.
- Grade 3: Severe AE, defined as limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death.

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on subject/event outcome at the time of the event. For example, the NCI CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

10.1.3. Causality Assessment

The Investigator should assess causal relationship between an AE and each of the Study Drugs (pembrolizumab and PLX3977) on the basis or his/her clinical judgment and the

following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
  - The AE follows a reasonable temporal sequence from Study Drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
  - The AE follows a reasonable temporal sequence from Study Drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

10.1.4. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in Study Drug dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Dose Reduced: The dosage of study product was reduced.
- 4 = Drug Interrupted: The study product was temporarily stopped.
- 5 =Dose Increased: The dosage of study product was increased.

10.1.5. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- 4 = Fatal
- 5 = Unknown

10.1.6. Other Action Taken for Event

- 1 = None.
  - No treatment was required.
- 2 = Medication required.
  - Prescription and/or OTC medication was required to treat the AE.
- 3 = Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- 4 = Other.

10.2. Serious Adverse Event Reporting–Procedure For Investigators

Any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study (see Section 10.1.1.2) that occurs to any subject from the time the informed consent is signed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor.

The contact information for the medical monitor for this study is presented below. The contact information for the central and any additional clinical laboratories, the coordinating Investigator for each member state/country, and CRO can be found in the Study Manual. A full list of Investigators is available in the Sponsor's Investigator database.

Medical Monitor: (Emergency Contacts)	[redacted] Plexxikon Inc. 91 Bolivar Drive, Berkeley, CA 94710 **Telephone**: [redacted] **Fax**: [redacted] **E-mail:** [redacted]m
SAE Reporting Contact	The Investigator will ensure that the SAE reporting form is completed on the eCRF or E-mailed/eFaxed to the following address within 24 hours of learning of the occurrence of any SAE. **SynteractHCR Safety SAE Facsimile** **Fax:** 760-268-6500 **Telephone:** [redacted] **Email:** safetyfax@synteracthcr.com

10.2.1. Notifying Regulatory Authorities, Investigators, IRB/EC, and Competent Authorities

Plexxikon and/or CRO will inform Investigators, IRBs or Ethics Committees, and regulatory authorities of any suspected unexpected serious adverse event reactions (SUSARs) occurring in other study centers or other Plexxikon studies of the investigational product, as appropriate per local reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the investigational product, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

10.3. Contraception

Pembrolizumab and PLX3397 may have adverse effects on a fetus in utero. Furthermore, it is not known if either drug has transient adverse effects on the composition of sperm. Therefore, nonpregnant, non-breast-feeding women may be enrolled only if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than ≥1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

The two 2 birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Note: hormonal contraceptives are contraindicated for triple-negative breast cancer.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 11.4. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

10.4. Pregnancy and Lactation and Reporting Requirements to Plexxikon

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the study. All

subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Study Reference Manual.

10.5. Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

10.6. Events of Clinical Interest (ECI)

Selected nonserious and SAEs are also known as ECI and must be recorded as such on the AE CRF/worksheets. For reporting, Plexxikon contact information can be found in the Investigator Trial File Binder (or equivalent).

ECI for this trial include:

1. An overdose of Sponsor's product, as defined in Section 10.11, which is not associated with clinical symptoms or abnormal laboratory results should be reported to Plexxikon or its designee within 24 hours either by electronic media or paper.
2. An elevated AST or ALT lab value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that ≥2 × ULN and, at the same time, an alkaline phosphatase (AP) lab value that <2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing should be reported to Plexxikon or its designee within 24 hours either by electronic media or paper.

   Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Study Reference Manual.

Subjects should be assessed for possible ECIs prior to each dose.

10.7. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at the study visits indicated in the Schedule of Events (Appendix 17.6). Collection, processing, labeling, handling, and shipment of samples will be outlined in the separate Laboratory Manual. Clinical laboratory evaluations will be performed as described in Appendix 17.5.

10.8. Vital Signs

Assessments of vital signs include blood pressure, heart rate, respiratory rate, and temperature (oral, axillary or tympanic, °F), height (at protocol-specified visits only), weight,). The subject is to be in the same position each time vital signs are assessed (i.e., supine, etc.) over the course of the study.

10.9. Electrocardiograms

ECGs should be performed pre-dose. Subjects should rest in the supine or semi-recumbent position for at least 5 minutes before each 12-lead ECG recording is started. The ECGs should be reviewed, signed, and dated by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. The Investigator is responsible for providing the interpretation of all ECGs. The results will include heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval.

10.10. Physical Findings and ECOG Performance Status

Physical findings will be assessed via a complete physical examination (at protocol-specified visits). All other physical examinations will be disease-specific and symptom-directed. Photography may be included as part of the physical examination for subjects who consent to the procedure. ECOG Performance Status (Appendix 17.3) will be assessed at protocol specified visits.

10.11. Overdose and Reporting of Overdose to Plexxikon

For purposes of this trial, an overdose of pembrolizumab will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. An overdose of PLX3397 for reporting as described in Section 11.6 will be defined as any dose exceeding the prescribed daily dose by ≥40%; smaller overdoses will be collected as described in the Study Reference Manual.

No specific information is available on the treatment of overdose of pembrolizumab or PLX3397. In the event of overdose, study treatment (either pembrolizumab or PLX3397) should be temporarily discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE is associated with ("results from") the overdose of Sponsor's product or vaccine, the AE is to be reported as an SAE even if no other seriousness criteria are met.

If a dose of Sponsor's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose will be reported as a nonserious ECI (Section 11.6), using the terminology "accidental or intentional overdose without adverse effect."

11. STATISTICAL METHODS

11.1. Analysis Sets

For each of the 2 phases of the study (Dose-escalation Phase, Expansion Phase), there will be 3 analysis sets:

- Safety Analysis Set: Defined as all subjects who received at least 1 dose of study treatment (i.e., PLX3397 or pembrolizumab). This is the primary analysis set for safety.
- Efficacy Analysis Set (EAS): Defined as all subjects in the Safety Analysis Set who met all enrollment criteria and received at least 1 dose of study treatment (i.e., PLX3397 or pembrolizumab). The EAS is the primary analysis set for efficacy.

In the Expansion Phase, efficacy will be described separately for each of the tumor type cohorts in Table 2.

11.2. General Statistical Considerations

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, and minimum and maximum values. Categorical variables will be summarized using frequency counts and percentages. In general, the baseline value for a variable is the last non-missing value before study treatment.

11.2.1. Dose-escalation Phase

The Dose-escalation Phase of the study will employ a standard 3+3 design in order to determine the MTD/MAD for PLX3397 (which will be the RP2D for future trials) when administered with pembrolizumab 200 mg IV every 3 weeks. As shown in Table 1, up to 4 dose levels of continuous PLX3397 dosing will be investigated. Alternative PLX3397 dose regimens at one or more of these dose levels also may be explored (see Section 3.1.1). Subjects will be treated and analyzed in cohorts of 3 to 6, and the dose level will be escalated if the clinical toxicity is acceptable.

11.2.2. Expansion Phase

Once the RP2D is determined, the Expansion Phase will be initiated to investigate the use of PLX3397 in combination with pembrolizumab in separate disease cohorts based on tumor type/subtype (Table 2). A key objective of this phase is to obtain preliminary estimates of disease response in each cohort. A truncated sequential probability ratio test for single-arm binary response studies will be employed in each of these cohorts (DOD RAC 2005). This sequential monitoring procedure establishes continuous boundary conditions to stop enrollment for either success (efficacy) or futility at any time up to the total prescribed sample size; hence, monitoring of response outcomes may be applied continuously for early closing of a cohort for success or futility using the sequential monitoring boundaries. Subjects will be evaluated for response until they discontinue treatment or until 6 months after the last subject is enrolled in the cohort, whichever occurs first. The study team will make decisions regarding early closing of a

cohort for success or futility. Since response rates to single-agent pembrolizumab therapy vary by disease type, there will be different sample sizes, operating characteristics and stopping rules for each cohort. Table 11 lists each tumor type of interest, with associated null rate and assumed true response rate under the alternative hypothesis, and the total sample size planned for each cohort to evaluate success or futility. The last two columns in the table list by cohort the total sample size and the minimum number of responders needed to conclude success for that total sample size (i.e., reject the null response rate).

Table 11. Sequential Monitoring Approach During Expansion Phase: Study PLX108-14

Tumor Type	Null Rate (%)	Assumed True Response Rate (%)	Number of Subjects When Monitoring to Start (Minimum)	For Total Sample Size	
				Total Number	Minimum No. Responders for Success Criterion
Melanoma (Tx-naïve)	40	70	7	23	15
Melanoma (1º progr.)	5	20	10	33	6
Melanoma (2º progr.)	10	30	10	33	9
NSCLC (non-squamous; EGFR and ALK wild-type) 1º progr. with anti-PD1/anti-PDL1 therapy	5	20	10	33	6
Ovarian	10	30	10	33	9
TNBC	15	35	9	38	12
SCCHN (1º progr. with anti-PD1/anti-PDL1 therapy)	5	20	10	33	6
Clear cell renal cell carcinoma (CCRCC)	20	40	13	48	17
PDA	5	20	10	33	6
Gastric	30	55	9	39	20
Glioblastoma multiforme (GBM)	5	20	10	33	6
GIST	10	30	10	33	9
High grade soft tissue sarcoma[a]	15	35	9	38	12
Cholangiocarcinoma	10	30	10	33	9
Totals	-	-	**137**	**483**	-

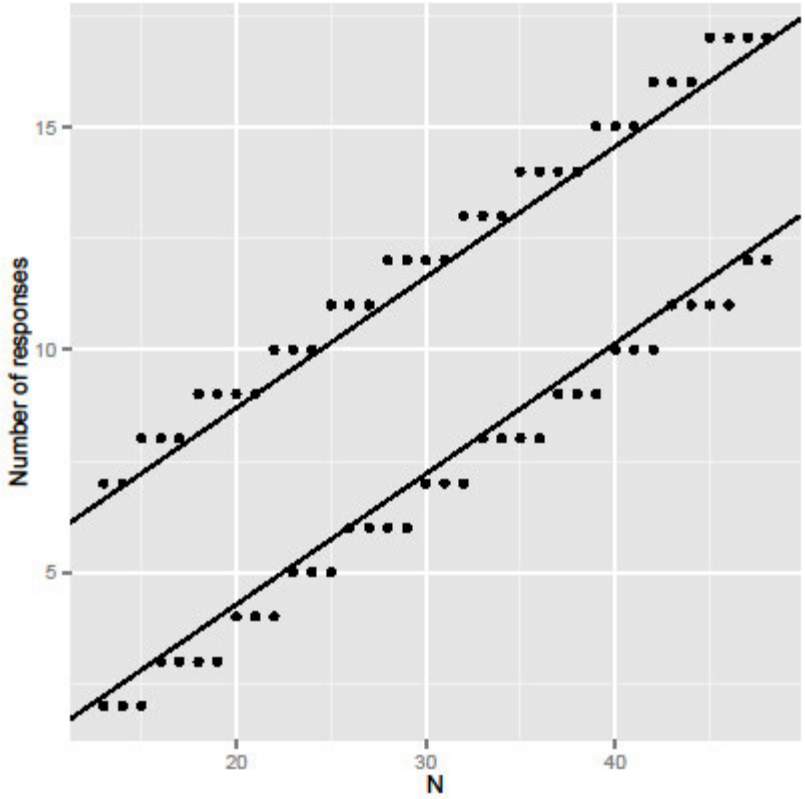
1º progr. = primary progressive; 2º progr. = secondary progressive; GIST = gastrointestinal stromal tumor; NSCLC = non-small-cell lung cancer; PDA = pancreatic ductal adenocarcinoma; SCCHN = squamous cell cancer of the head and neck; TNBC = triple-negative breast cancer; Tx = treatment

[a] High grade soft tissue sarcoma includes undifferentiated pleomorphic sarcoma and liposarcoma.

Depending on the null response rate, target response rate, minimum (monitoring start point) and total sample sizes, alpha level (one-sided) and power, this sequential monitoring procedure sets up criteria for the number of responders required to indicate either efficacy or futility continuously, i.e., for any given number of subjects who enter the cohort. As an example, the stopping conditions for the scenario of null rate of 20%, target rate of 40%, minimum and total of 13 and 48 evaluable subjects (respectively), one-sided alpha of 0.05 and power of 80% is presented in Figure 2. This scenario shows that at least 17 responders are required for success in these indications with a total sample size of 48.

For all tumor types/subtypes, one-sided alpha of 0.05 and 80% power were used for calculating boundary conditions. The stopping criteria for the numbers of responders for either efficacy or futility, for the other tumor subtypes will be displayed in the statistical analysis plan (SAP).

Figure 2: Stopping Conditions for Null Response Rate of 20% versus Target Rate of 40%: Expansion Phase



Note: Scenario: null rate of 20%, target rate of 40%, minimum and total of 13 and 48 evaluable subjects (respectively), one-sided alpha of 0.05 and power of 80%.

11.2.3. Efficacy Analyses

In general, efficacy in the Expansion Phase will be evaluated separately within each tumor-type cohort. Disease response will be evaluated using RECISTv1.1 criteria using the FAS. ORR is defined as the proportion of subjects who achieve a best disease

response of either CR or PR based on RECIST 1.1 criteria. Patients who discontinue study therapy due to clinical progression, radiographic progression or death without the required tumor assessments will be considered to be non-responders in the ORR calculation. The efficacy analysis will include all subjects with baseline tumor measurements who received at least one dose of study treatment. The primary analysis of ORR will be performed with the FAS in each tumor-type cohort in the Expansion Phase. The point estimate, confidence interval (CI), and adjusted p-values for testing whether the observed ORR is statistically greater than the specified null rate will be provided. Exact methods for binary, sequential data will be employed for the analysis (DOD RAC 2005). Details of the analysis will be included in a separate SAP.

PFS is defined at the time from start of Study Drug to date of disease progression or death due to any cause. For PFS and any other time-to-event analyses, the Kaplan-Meier product limit method will be used to compute the estimate and 95% CI of the median and 25th and 75th percentiles. The number of responders, the number with subsequent disease progression, and the number with censored values will be displayed as well.

The proportion of irRECIST-based responses will be tabulated with 95% CIs.

11.2.4. Power and Sample Size

For the Dose-escalation Phase of the study, 3 to 6 subjects will be accrued per dose level or regimen in order to insure the safety and tolerability. The number of subjects is not based on statistical power considerations.

The Expansion Phase of the study will enroll a minimum of 7 to 13 subjects in each tumor type cohort as the monitoring start point. The total sample size is shown in Table 11. A one-sided alpha of 0.05 and 80% power were required for each cohort. Once the prescribed minimum number of efficacy-evaluable subjects in a cohort have had at least one post-baseline response assessment, a sequential monitoring procedure will be used to evaluate for efficacy and futility simultaneously based on the number of subjects with a response according to the rules outlined in Figure 2 (for the case of a null vs. target rates of 20% and 40% as an example). For other null and target rates, the corresponding figure will be provided in the SAP.

Depending on the enrollment rate, it is possible that more than the minimum number of subjects may be enrolled prior to the first evaluation of efficacy or futility. Enrollment is expected to be continuous and will not be held. Once the minimum number of subjects are evaluable for confirmed or unconfirmed response, subsequent rules for pausing enrollment and future evaluations will be based on the boundaries identified by the sequential monitoring procedure until the total sample size has been enrolled.

The calculation is based on the binomialSPRT function in the gsDesign package and is carried out using R version 3.1.3 (R Core Team 2015).

11.2.5. Subjects Who Continue From the Dose-escalation Phase

Subjects who participated in the Dose-escalation Phase can continue at the dose determined for their cohort, assuming that dose is pharmacologically active, or can be

titrated up to the RP2D, at the discretion of the Investigator. These subjects will be analyzed descriptively.

11.2.6. Study Population Data

Subject disposition will be summarized by each dose cohort and for total in the Dose-escalation Phase and by tumor type and for total in the Expansion Phase for the Efficacy Analysis Set. The total number of subjects for each defined analysis population will also be tabulated.

The demographic and baseline characteristics will be summarized descriptively for the Safety Analysis Set. Study treatment exposure and study duration will be summarized using descriptive statistics for the Safety Analysis Set.

All study data will be presented in by-subject data listings.

11.3. Analyses

11.3.1. Analysis of Primary Endpoint

The primary endpoint, defined in Section 3.1.4.1, is restated below:

- To establish the RP2D of PLX3397 in combination with pembrolizumab for future trials. The RP2D is defined as the MTD or MAD of PLX3397. The MTD is defined as the dose level below the one at which more than 1 of 6 subjects experience DLT in Cycle 1 (1 cycle = 42 days). The planned MAD is defined as PLX3397 administered orally at 1000 mg/day as a split dose (Table 1).

The 3+3 design allows for determination of the MTD/MAD, based on the incidence of DLT during Cycle 1. DLTs are defined in Section 3.1.7.1. The Rules for Dose-escalation are provided in Section 3.1.7.2. The MTD is defined in Section 3.1.7.3. The probabilities of dose based on true DLT risk in the 3+3 design are summarized in Table 12.

Table 12. Probabilities of Dose Escalation Based on True DLT Risk in the 3+3 Design: Statistical Basis for Dose Escalation

True Incidence of Dose-limiting Toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

DLT = dose-limiting toxicity

11.3.2. Analyses of Secondary Endpoints

The secondary endpoints, defined in Section 3.1.4.2, are restated below:

- To evaluate the safety and tolerability of the combination of pembrolizumab and PLX3397, based on the incidence of AES, as graded by the NCI CTCAE.
- To evaluate ORR by RECISTv1.1 guidelines (Appendix 17.4), relative to the assumed historical control rate for pembrolizumab, for each of the tumor types (Table 2) in subjects treated with the RP2D of PLX3397 for the combination

of PLX3397 and pembrolizumab. Subjects with each of the tumor types will also be analyzed by RECISTv1.1 for PFS. See Section 11.2.3 and the SAP for details of these analyses.

11.3.3. Analysis of Exploratory Endpoints

The exploratory endpoints and methods for analyzing them, defined in Section 3.1.4.3, are restated below:

- To evaluate ORR by irRECIST guidelines (see the irRECIST Tip Sheet, provided in the Study Reference Manual), relative to the assumed historical control rate for pembrolizumab, for each of the tumor types (Table 2) in subjects treated with the RP2D of PLX3397 for the combination of PLX3397 and pembrolizumab (Expansion Phase). Subjects with each of the tumor types will also be analyzed by irRECIST for PFS.
- To evaluate ORR and PFS by RECISTv1.1 guidelines (Appendix 17.4) descriptively by cohort for subjects in the Dose-escalation Phase. The PFS distributions for each tumor type will be estimated using the Kaplan-Meier method (Section 11.2.3).
- To determine effects of the combination of PLX3397 and pembrolizumab on multiple biomarkers of disease or treatment, through analysis of available paired tumor biopsy samples using methods that include but are not limited to Nanostring and IHC of intratumoral CD68+ macrophages and CD8+ T-cells. Mandatory baseline (up to -2 days) and Day 29 (± 3 days) or Day 22 (± 3 days) for intermittent, post-treatment biopsies will be collected in the Expansion Phase, unless deemed medically unsafe by the Investigator. Biopsies will be optional in Dose-escalation.

11.3.3.1. Safety and Tolerability

The safety and tolerability of the combination of pembrolizumab and PLX3397 will be determined by the incidence of AEs that occur throughout dosing of one or both study medications. Frequencies of toxicities will be summarized based on the NCI CTCAE, version 4.03. AEs that occur will be reported for and described in terms of incidence and severity.

11.3.3.2. Evaluation of the Objective Response Rate in the Expansion Phase

To obtain preliminary estimates of efficacy, the Expansion Phase will be conducted in several tumor types described in Table 2. For each tumor type, the objective is to estimate the ORR, defined as proportion of subjects who achieve a CR or PR among all subjects, relative to the assumed historical control ORR. Response to study treatment will be evaluated by RECISTv1.1 (Appendix 17.4).

For each of the subject populations (defined by tumor type; see Table 2), a truncated sequential probability ratio test for single-arm binary response studies will be used. A one-sided alpha of 0.05 and 80% power will be used for all tumor types for calculating

boundary conditions. In addition, the monitoring start point, total sample size (range 23 to 48), null rate, and target rate are stated for each tumor type in Table 11.

11.3.4. Exploratory Pharmacology Studies of Drug Activity

To confirm drug target activity, baseline (up to -2 days) and 28-day (± 3 days) biopsies will be performed on subjects recruited during the Expansion Phase, who will be treated at the RP2D. Immunohistochemistry (IHC) and pathologist scoring of percent positive T-cells and percent positive macrophage in tumor will be conducted to determine T-cell infiltration and macrophage depletion. Transformation of quantitative variable will be performed to achieve normality if possible. A paired t-test or Wilcoxon signed-rank test will be used to determine if there is a statistically significant change.

11.3.5. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be summarized for the maximum and minimum post-treatment values and the values at the End-of-Treatment visit.

Abnormal clinical laboratory results will be graded according to NCI CTCAE, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting by treatment group the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, may be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

11.3.6. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the End-of -Treatment visit.

11.3.7. Electrocardiogram Analyses

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation, as well as for the change from baseline. The baseline value is defined as the last nonmissing value before the initial administration of study treatment. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (e.g., QTc ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms) and QT_cF maximum changes from baseline (>30 and >60 ms) over all post-treatment evaluations will be summarized. ECG data will also be presented in the data listings.

11.3.8. Physical Finding Analyses

Physical examination data will be listed.

11.4. Interim Analyses

During the Expansion Phase, the number of responders will be monitored continuously in each tumor-type cohort, once a minimum number of subjects have been enrolled in that cohort. Enrollment may be stopped within a cohort for futility or efficacy based on the stopping criteria described in Section 11.2.2.

11.5. Data Monitoring Committee (DMC)

Generally, a DMC will not be used for this study. This is an open-label, Phase I/II study, and the Sponsor Medical Monitor (MM) and individual Investigators will have access to the safety data on a regular basis during the study and conduct regularly scheduled teleconferences to discuss the available safety data. These teleconferences will serve as a mechanism for determination of unanticipated problems involving risks to subjects or others; an additional mechanism is the reporting of SAEs to the IRB and/or health authorities (Section 11.2).

11.5.1. Dose-escalation Phase

The Sponsor MM and Investigators will discuss data on all subjects on an approximately biweekly basis and also meet at the end of each treatment cohort to discuss and evaluate all of the available safety data. At dose escalation teleconferences, the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the first cycle of treatment, and if applicable, PK data) for each subject in the current dose cohort will be described in detail. Updated safety data on other ongoing subjects, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. The Sponsor MM and the Investigators must reach a consensus on whether to declare MTD, escalate the dose, de-escalate the dose and/or study an additional cohort of subjects at the current or an intermittent regimen.

11.5.2. Expansion Phase

Due to the exploratory nature of this phase I/II study an independent DMC will not be constituted for the Expansion Phase of this study. Instead, a review of the safety data will be performed at periodic interim data safety reviews by the Sponsor MM and the Investigators in a data review meeting with the first review meeting occurring when about 30 subjects in the Expansion Phase have received at least about 1 cycle of study treatment. There will also be regularly scheduled teleconferences between the Sponsor MM and participating Investigators to review ongoing data for active subjects.

It is envisioned that the team may make the following recommendations at each of the interim data safety reviews:

- No safety or efficacy issues, ethical to continue the trial as planned
- Serious safety concerns requiring modification of dosing regimens or guidelines (e.g., one-third occurrence of DLT as described in Section 3.1.7.2 and Section 3.1.9.1) or precluding further study treatment, regardless of efficacy

In addition, the best overall response for each subject will be derived from the overall lesion response assessments recorded in the eCRF to calculate the probability of success or futility estimate for the respective tumor type per the truncated sequential monitoring approach (Section 11.2.2 and Figure 2). The first such interim will occur for a particular tumor type once the minimum number of subjects has been treated within the cohort according to the statistical plan. For each cohort, this will be after 7 to 10 subjects have been treated (Table 11). Thereafter, additional interim data safety reviews will occur after additional groups of 7 to10 subjects have been treated. The tumor type cohort or study is terminated due to lack of significant activity

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The Plexxikon monitor or appropriately qualified designee and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., CRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for reviewing the CRFs against source documents for completeness and accuracy. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. The monitor will also ensure study essential documents are up to date and filed appropriately.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the Sponsor’s audit plans, this study may be selected for audit by representatives from Sponsor. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2. Data Collection

eCRF completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. eCRF will be completed, reviewed and e-signed by the Investigator.

The Investigator will e-sign according to the study data flow. These signatures will indicate that the Investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Any data recorded on the eCRF will be collected and included in the database according to Clinical Data Interchange Standards Consortium standards and subjected to the same procedures as other data.

12.3. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications in the Data Management Plan. Data will be vetted both electronically and manually. For electronic CRFs (eCRFs), the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies.

SAEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA.

12.4. Study Documentation and Storage

The Investigator will maintain a Delegation Log of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed CRFs, informed consents, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to

commencing a clinical study, and all correspondence to and from the IEC/IRB and the Sponsor.

- Records related to the Investigational Product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

12.5. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13. COMPLIANCE STATEMENT, ETHICS AND REGULATORY COMPLIANCE

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and the following applicable regulatory requirement:

- FDA GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56, and 312 as appropriate

13.1. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs/eCRFs or other documents submitted to Plexxikon, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to Plexxikon or appropriately qualified designee (e.g., signed Informed Consent Forms [ICFs]) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC or IRB direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is

obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

13.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by Code of Federal Regulations Title 21, Part 312.62. The ICF should be signed and personally dated by the subject or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

If the subject or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Suggested model text for the ICF for the study and any applicable subparts (genomic, pharmacokinetic, etc.) and assent forms for pediatric subjects (if applicable) are provided in the Sponsor ICF template for the Investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Clinical Study Manager. An additional consent is required for the Health Insurance Portability and Accountability Act.

13.3. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any subject Diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., advertisements), information about

payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan.

The Investigator must submit and, where necessary, obtain approval from the IRB and/ or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Plexxikon or its designee, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will insure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

14. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that Plexxikon has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of Plexxikon Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/EC within five working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

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17. APPENDICES

17.1. Drugs Clearly Associated with the Risk of Torsades de Pointes and QT Prolongation

Anti-arrhythmics	Anti-cancer
- Amiodarone	- Arsenic trioxide
- Disopyramide	- Vandetanib
- Dofetilide	
- Dronedarone	Anti-depressants, SSRIs
- Flecainide	- Citalopram
- Ibutilide	- Escitalopram
- Procainamide (oral off US market)	
- Quinidine	Antihistamines
- Sotalol	- Astemizole (removed from US market)
- Ritonavir	- Terfenadine (removed from US market)
- Indinavir	
- Nelfinavir	Anti-malarials
	- Chloroquine
Anti-retrovirals	- Halofantrine
- Ritonavir	
- Indinavir	Antilipemic
- Nelfinavir	- Probucol (removed from US market)
	- Ondansetron
Antimicrobials	
- Azithromycin	Opiates
- Ciprofloxacin	- Levomethadyl acetate (removed from US market)
- Clarithromycin	- Methadone
- Erythromycin	
- Grepafloxacin (off market worldwide)	Anesthetics, general
- Levofloxacin	- Propofol
- Moxifloxacin	- Sevoflurane
- Sparfloxacin (removed from US market)	
- Pentamidine	Others
- Fluconazole	- Cisapride (removed from US market)
	- Cocaine
Anti-psychotics	- Anagrelide
- Haloperidol	- Bepridil (removed from US market)
- Mesoridazine (removed from US market)	- Domperidone (on non US market)
- Pimozide	
- Thioridazine	
- Chlorpromazine	
- Droperidol	
- Sulpiride (on non-US market)	

17.2. CYP3A4 Inhibitors and Inducers

Common CYP3A4 Inhibitors

The following lists describe medications and foods which are common inhibitors of CYP3A4. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

Protease Inhibitors	Others
indinavir nelfinavir ritonavir	clarithromycin erythromycin gemfibrozil itraconazole ketoconazole nefazodone verapamil telithromycin fluconazole chloramphenicol aprepitant trimethoprim thiazolidinedione montelukast quercetin
Food/Juice	
grapefruit juice	

Common CYP3A4 Inducers

The following lists describe medications which are common inducers of CYP3A4. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A4.

HIV Antivirals	Others
efavirenz nevirapine etravirine	barbiturates carbamazepine glucocorticoids modafinil phenobarbital phenytoin rifampin St. John's Wort rifabutin oxcarbazepine cyproterone

17.3. Eastern Cooperative Oncology Group Performance Status

ECOG PERFORMANCE STATUS[a]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	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	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a] As published in Oken 1982.

The ECOG Performance Status is in the public domain and is therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Revised: July 27, 2006

17.4. Response Evaluation Criteria for Solid Tumors, version 1.1

Below are the RECISTv1.1 criteria as developed by Eisenhauer, et al. 2009.

Measurability of Tumor at Baseline

Definitions: At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows.

Measurable Tumor Lesions

Tumor lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm 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. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

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 non-cystic 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.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Still, non-contrast CT is preferred over chest X-ray.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should

be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least 1 measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

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

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only 1 or 2 organ sites involved a maximum of 2 (1 site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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*. If lymph nodes are to be included in the sum, then as noted above, 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.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- *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 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 1 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.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. CRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become *'too small to measure'*: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may

report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below the measurable limit (BML) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: **in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: this circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either 1 the 'best overall response'. This is described further below.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 13 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, Table 14 is to be used.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

If 1 or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the subject is not evaluable. Similarly, if 1 or more non-target lesions are indicated as "not assessed," the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Best overall response: All time points

The *best overall response* will be determined by statistical programming once all the data for the subject is known.

Table 13. Time Point Response: Patients 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; NE = inevaluable; PR = partial response; PD = progressive disease; SD = stable disease

Table 14. Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PR = partial response; PD = progressive disease; SD = stable disease

[a] Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 15. Best Overall Response When Confirmation of CR and PR is Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PR = partial response; PD = progressive disease; SD = stable disease

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of 'zero' on the CRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The

objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Table 13, Table 14, and Table 15.

Conditions that define "early progression, early death, and inability to evaluate" are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

17.5. Clinical Laboratory Evaluations

Blood samples will be obtained for analyses of the following parameters:

Comprehensive Serum Chemistry Panel

- Sodium
- Potassium
- Chloride
- CO_2
- Calcium
- Phosphorus
- Glucose[a]
- Blood urea nitrogen (BUN)
- Creatinine
- Total protein
- Albumin
- Uric acid
- Lactate dehydrogenase
- Magnesium

[a] Fasting is recommended but not required.

Thyroid Function Panel

- T3 or FT3 (choose one for any individual subject)
- FT4, TSH

Liver Function Tests

- AP
- AST
- Alanine aminotransferase (ALT)
- Gamma-Glutamyl Transferase (GGT)
- Total bilirubin
- Direct bilirubin

Biomarkers of Drug Effects on Liver

- miR122
- HMGB1 (native and acetylated)
- Cytokeratin (18 full-length and caspase-cleaved)

Hematology

- RBC count
- White blood cell (WBC) count with differential
- Platelet count
- Hemoglobin
- Hematocrit

Hepatitis Panel

- HBV surface antigen test and HCV antibody test

Coagulation Studies

- Prothrombin time (PT), aPTT, and INR

Serum Pregnancy Test (β-hCG): women of child-bearing potential

Urinalysis (dipstick and microscopic analysis)

Urine samples will be obtained for analysis of the following parameters:

- pH
- Protein/albumin
- Glucose/sugar
- Ketones/acetone
- Hemoglobin/blood
- RBC, WBC, epithelial cells, bacteria, casts, crystals

17.6. Schedule of Events for Protocol PLX108-14: Dose-escalation and Expansion Phases

Trial Period	Screening	Treatment													Post-Treatment Follow-up	
Cycle		1						2				3 and Beyond		End of Treatment	Safety Follow-up	SAE Follow-up[a]
Day	-28 to -1	1[c]	8	15	22	29	36	1	8	15	22	1	22	At Time of DC	28 Days Post-DC	Every 12 Weeks[b]
Scheduling Window Days	±3	-2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±7	±7
Eligibility Criteria	X															
Informed Consent	X															
Medical History	X															
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Compliance			X	X	X	X	X	X			X	X	X	X		
Post-treatment DC anticancer therapy status														X	X	
Clinical Procedures																
Full Physical Examination (including height, only at Screening)	X							X				X		X		
Directed Physical Examination		X	X	X	X	As clinically indicated										
ECOG Performance Status	X	X						X				X		X		
Height	X															
Vital Signs (including weight)	X	X	X	X	X	X	X	X			X	X	X	X	X	
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	
Laboratory Procedures/Assessments[i]																
CBC with Differential	X	X	X	X	X	X	X	X			X	X	X	X	X	
HBV, HCV testing	X															
Coagulation Studies (PT, aPTT, and INR)	X															
Urinalysis (with microscopic exam)	X	X			X			X				X		X	X	
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X			X	X	X	X	X	
Liver Function Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exploratory Biomarkers (Liver effect biomarkers)[c,d]		X	X	X	X	X								X		
MDSC[c]		X		X												

Trial Period	Screening	Treatment													Post-Treatment Follow-up	
Cycle		1						2				3 and Beyond		End of Treatment	Safety Follow-up	SAE Follow-up[a]
Day	-28 to -1	1[c]	8	15	22	29	36	1	8	15	22	1	22	At Time of DC	28 Days Post-DC	Every 12 Weeks[b]
Scheduling Window Days	±3	-2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±7	±7
CA-125[k]	X	X						X				X		X		
Thyroid Function Panel[e]		X						X				X			X	
Pregnancy Test (serum β-hCG)[f]	X	X														
ECG	X	X		X				X				X		X		
Drug Dispensation, Administration, and Associated Analyses																
Pembrolizumab Administration		X			X			X			X	X	X			
PLX3397 Administration	Subjects will self-administer PLX3397 at home as 2 split doses, administered ~12 hours apart. On days where PLX3397 PK samples are collected, subjects will bring their morning dose of PLX3397 to the clinic and receive it under the supervision of study site staff.															
Pharmacokinetics	Please refer to Table 10															
Anti-pembrolizumab Antibodies (ADA)																
Efficacy Measurements																
Tumor Imaging[g]	X	Every 9 weeks ± 7 days												X		
Digital Photography: Cutaneous Lesions	X	As clinically indicated														
Pharmacodynamic Assessments																
Tumor Tissue Collection (i.e., Biopsies)[h]	X					X										
Exploratory Pharmacology Blood Sample Collection		X			X	X								X		

ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; β-hCG = beta human chorionic gonadotropin; DC = date of last dose; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FDG-PET= [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography-computer tomography (PET/CT); HBV = hepatitis B virus; HCV; hepatitis C virus; INR = international normalized ratio; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; PT = prothrombin time; SAE = serious adverse event

[a] SAE follow-up will include disease status: scheduled visit on 12-and 24-week follow-up; phone call or visit every 12 weeks thereafter.

[b] Post 24-week follow-up via telephone: Serious Adverse Event (SAE) monitoring only.

[c] Treatment period, Cycle 1: Samples for laboratory evaluation should be collected prior to dosing with pembrolizumab and PLX3397.

[d] Liver effect biomarkers at scheduled visits, also if ALT or AST are Grade 2 or higher and 5–8 days after PLX3397 dose hold or interruption.

[e] Thyroid Function Test to be performed every 6 weeks. If TSH is not within normal limits at baseline, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits. If TSH, T3 and T4 are all abnormal, the thyroid function tests should be repeated Q3 weeks to be sure there is no change that meets autoimmune thyroiditis.

[f] For women of childbearing potential only: To be performed within 72 hours prior to Cycle 1 Day 1. Monthly pregnancy testing should be conducted as per local regulations where applicable.

[g] Per irRECIST used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease (see the irRECIST Tip Sheet, provided in the Study Reference Manual). FDG-PET should be assessed at screening and C2D22 for GIST subjects only.
Tumor Imaging Screening and End of Treatment (EOT) visit window ± 7 days.

[h] Paired biopsies are optional in Dose-escalation, and required in the Expansion Phase (Baseline, Day 29) but optional for Expansion Phase at EOT, unless deemed medically unsafe by the Investigator. If PLX3397 study drug interruption occurs during the week prior to the on-treatment biopsy, the Medical Monitor should be contacted.

[i] Screening labs required for Inclusion Criteria #10: these laboratory tests should be performed within 10 days of C1D1.

[j] SAEs are collected through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor.

[k] CA-125 results to be collected per institutional standard of care for ovarian tumor type: e.g., two pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of C1D1; subsequent samples on the first day of each cycle starting with Cycle 2 Day 1 and at the End-of-Study Visit.

17.7. Schedule of Events for Protocol PLX108-14: Dose-escalation and Expansion Phase: Cohort Intermittent PLX3397 Administration

Trial Period	**Screening**	**Treatment**																**Post-Treatment Follow-up**	
Cycle		**1**						**2**					**3 and Beyond**				**End of Treatment**	**Safety Follow-up**	**SAE Follow-up[a]**
Day	**-28 to -1**	**1[c]**	**8**	**15**	**22**	**29**	**36**	**1**	**8**	**15**	**22**	**29**	**1**	**8**	**22**	**29**	**At Time of DC**	**28 Days Post-DC**	**Every 12 Weeks[b]**
Scheduling Window Days	±3	-2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±7	±7
Eligibility Criteria	X																		
Informed Consent	X																		
Medical History	X																		
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Compliance			X	X	X	X	X		X			X		X		X	X		
Post-treatment DC anticancer therapy status																	X	X	
Clinical Procedures																			
Full Physical Examination (including height, only at Screening)	X								X					X			X		
Directed Physical Examination		X	X	X	X								As clinically indicated						
ECOG Performance Status	X	X							X					X			X		
Height	X																		
Vital Signs (including weight)	X	X	X	X	X				X			X		X		X	X	X	
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	
Laboratory Procedures/ Assessments[k]																			
CBC with Differential	X	X	X	X	X	X	X	X			X		X		X		X	X	
HBV, HCV testing	X																		
Coagulation Studies (PT, aPTT, and INR)	X																		
Urinalysis (with microscopic exam)	X	X			X			X					X				X	X	
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X			X		X		X		X	X	

Trial Period	**Screening**	**Treatment**																**Post-Treatment Follow-up**	
Cycle		**1**						**2**					**3 and Beyond**				**End of Treatment**	**Safety Follow-up**	**SAE Follow-up[a]**
Day	**-28 to -1**	**1[c]**	**8**	**15**	**22**	**29**	**36**	**1**	**8**	**15**	**22**	**29**	**1**	**8**	**22**	**29**	**At Time of DC**	**28 Days Post-DC**	**Every 12 Weeks[b]**
Scheduling Window Days	±3	-2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±7	±7
Liver Function Tests	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	
Exploratory Biomarkers (Liver effect biomarkers)[c,d]		X	X	X	X	X											X		
MDSC[c]		X		X															
CA-125[m]	X	X						X					X				X		
Thyroid Function Panel[e]		X							X					X				X	
Pregnancy Test (serum β-hCG) [f]	X	X																	
ECG	X	X		X	X			X					X				X		
Drug Dispensation, Administration, and Associated Analyses																			
Pembrolizumab Administration		X			X			X			X		X		X				
PLX3397 Administration			X	X		X	X		X			X		X		X			
	Beginning 7 days (Day 8) after pembrolizumab infusion, subjects will self-administer PLX3397 at home as 2 split doses, administered ~12 hours apart until the day before the next pembrolizumab administration (Day 22). On days where PLX3397 PK samples are collected, subjects will bring their morning dose of PLX3397 to the clinic and receive it under the supervision of study site staff.																		
PLX3397 PK Assessments		X			X		X[i]	X					X						
Anti-pembrolizumab Antibodies (ADA) and pembrolizumab pharmacokinetics	Please refer to Table 10																		
Efficacy Measurements																			
Tumor Imaging[g]	X	Every 9 weeks ± 7 days															X		
Digital Photography: Cutaneous Lesions	X	As clinically indicated																	
Pharmacodynamic Assessments[h]																			
Tumor Tissue Collection (i.e., Biopsies)[j]	X				X														

Trial Period	Screening	Treatment															Post-Treatment Follow-up	
Cycle		1						2					3 and Beyond				End of Treatment	Safety Follow-up	SAE Follow-up[a]
Day	-28 to -1	1[c]	8	15	22	29	36	1	8	15	22	29	1	8	22	29	At Time of DC	28 Days Post-DC	Every 12 Weeks[b]
Scheduling Window Days	±3	-2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±7	±7
Exploratory Pharmacology Blood Sample Collection	X				X	X											X		

ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; β-hCG = beta human chorionic gonadotropin; DC = date of last dose; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV; hepatitis C virus; INR = international normalized ratio; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; PT = prothrombin time; SAE = serious adverse event

[a] SAE follow-up will include disease status: Scheduled visit on 12-and 24-week follow-up; phone call or visit every 12 weeks thereafter.

[b] Post 24-week follow-up via telephone: Serious Adverse Event (SAE) monitoring only.

[c] Treatment period, Cycle 1: Samples for laboratory evaluation should be collected prior to dosing with pembrolizumab.

[d] Liver effect biomarkers at scheduled visits, also if ALT or AST are Grade 2 or higher and 5–8 days after PLX3397 dose hold or interruption.

[e] Thyroid Function Test to be performed every 6 weeks. If TSH is not within normal limits at baseline, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits. If TSH, T3 and T4 are all abnormal, the thyroid function tests should be repeated Q3 weeks to be sure there is no change that meets autoimmune thyroiditis.

[f] For women of childbearing potential only: To be performed within 72 hours prior to Cycle 1 Day 1. Monthly pregnancy testing should be conducted as per local regulations where applicable.

[g] Per irRECIST used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease (see the irRECIST Tip Sheet, provided in the Study Reference Manual).
Tumor Imaging Screening and End of Treatment (EOT) visit window ± 7 days.

[h] If entering the study with a PLX3397 run-in, baseline biopsy and exploratory biomarker collection will be taken at Screening before starting PLX3397.

[i] C1D36 requires PLX3397 predose trough PK sample drawn at -30 minutes (± 15 minutes) and detailed PK sampling drawn post dose at 30 minutes (± 15 minutes), 1, 2, 4, and 6 hours (± 30 minutes). All other visits are for trough levels, i.e., approximately 30 min before the morning dose or 12 hours after the PLX3397 evening dose taken the day before the clinic visit.

[j] Paired biopsies are optional in Dose-escalation and required in the Phase 2 Expansion, unless deemed medically unsafe by the Investigator. If PLX3397 study drug interruption occurs during the week prior to the on-treatment biopsy, the Medical Monitor should be contacted.

[k] Screening labs required for Inclusion Criteria #10: these laboratory tests should be performed within 10 days of C1D1.

[l] SAEs are collected through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor.

[m] CA-125 results to be collected per institutional standard of care for ovarian tumor type: e.g., two pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of C1D1; subsequent samples on the first day of each cycle starting with Cycle 2 Day 1 and at the End-of-Study Visit.

17.8. Schedule of Events for Protocol PLX108-14: Run-in with PLX3397 Before Combination with Pembrolizumab (C1D1)

Trial Period	Screening	Run-in		Treatment
Day (relative to C1D1)	**-42 to -15**	**-14**	**-7**	**C1D1[d]**
Scheduling Window Days	±3	-2	±3	-2
Eligibility Criteria	X	X		
Informed Consent	X			
Medical History	X			
Concomitant Medication Review	X	X	X	X
Study Drug Compliance			X	X
Clinical Procedures				
Full Physical Examination	X			
Directed Physical Examination		X	X	X
ECOG Performance Status	X	X		
Height	X			
Vital Signs (including weight)	X	X	X	X
AE Monitoring	X	X	X	X
Laboratory Procedures/Assessments[h]				
CBC with Differential[a]	X	X	X	X
HBV, HCV testing	X			
Coagulation Studies (PT, aPTT, and INR)[a]	X			
Urinalysis (with microscopic exam)	X	X		X
Comprehensive Serum Chemistry Panel[a]	X	X	X	X
Liver Function Tests[a]	X	X	X	X
Exploratory Biomarkers (Liver effect, MDSC)[a]		X	X	X
Pregnancy Test (serum β-hCG)[b]	X	X		X
ECG	X	X		X
PLX3397 Administration[c]		X	X	
PLX3397 Pharmacokinetics[e]				X

Trial Period	Screening	Run-in		Treatment
Day (relative to C1D1)	**-42 to -15**	**-14**	**-7**	**C1D1[d]**
Scheduling Window Days	±3	-2	±3	-2
Efficacy Measurements				
Thyroid Function Panel[f]				X
Tumor Imaging	X			
Digital Photography: Cutaneous Lesions	X			
Pharmacodynamic Assessments				
Tumor Tissue Collection (i.e., Biopsies[g])	X			
Exploratory Pharmacology Blood Sample Collection	X			

aPTT = activated partial thromboplastin time; β-hCG = beta human chorionic gonadotropin; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV; hepatitis C virus; INR = international normalized ratio

[a] Treatment period: Samples for laboratory evaluation should be collected prior to dosing with PLX3397.

[b] For women of childbearing potential only: To be performed within 72 hours prior to first dose of PLX3397. Monthly pregnancy testing should be conducted as per local regulations where applicable.

[c] Subjects will self-administer PLX3397 at home from Days -14 to -1as 2 split doses, administered ~12 hours apart each day. However, on days when clinical visits are scheduled, subjects will bring their morning dose of PLX3397 to the clinic and receive it under the supervision of study site staff.

[d] C1D1 defined as day of first pembrolizumab dose.

[e] PLX3397 trough PK sample.

[f] Thyroid Function Test to be performed every 6 weeks. If TSH is not within normal limits at baseline, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.

[g] Paired biopsies are optional in Dose-escalation and required in the Phase 2 Expansion, unless deemed medically unsafe by the Investigator. If PLX3397 study drug interruption occurs during the week prior to the on-treatment biopsy, the Medical Monitor should be contacted.

[h] Screening labs required for Inclusion Criteria #10: these laboratory tests should be performed within 10 days of C1D1.