CLINICAL STUDY PROTOCOL

Protocol Number:	PLX108-13
Title:	Phase I/II Open Label, Multicenter Study of PLX3397 in Patients with Unresectable or Metastatic KIT-mutated Melanoma
Indication:	Unresectable stage III or stage IV KIT-mutated melanoma
Phase:	I/II
Sponsor:	DAIICHI SANKYO CO., LTD.

Protocol History:

Date/Version:

VERSION 9.0 25 FEB 2020
VERSION 8.0 11 SEP 2018
VERSION 7.0 27 DEC 2017
VERSION 6.0 27 MAY 2017
VERSION 5.0 (17 November 2016/Amendment 4)
VERSION 4.0 (06 September 2016/Amendment 3)
VERSION 3.0 (04 August 2016/Amendment 2)
VERSION 2.0 (16 June 2016/Amendment 1)
VERSION 1.0 (9 October 2014/Original)

Confidentiality Statement

PHASE I/II OPEN LABEL, MULTICENTER STUDY OF PLX3397 IN PATIENTS WITH UNRESECTABLE OR METASTATIC KIT-MUTATED MELANOMA

Sponsor Approval:

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

[redacted]
Print Name

Signature

Clinical Study Lead
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 Council for Harmonisation 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.

<<Insert Name>>
Print Name

Signature

<<Insert Title>>
Title

Date (DD MMM YYYY)

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GLOBAL AMENDMENT, PROTOCOL VER 9.0

Amendment Rationale:

The main purpose of this amendment is to update the safety information for pexidartinib and to revise the dose modification criteria.

Changes to the Protocol:

Please refer to the comparison document for protocol version 8.0 (dated 11 Sep 2018) vs. protocol version 9.0 (dated 25 Jan 2020) for actual changes in-text. The summary of changes below is a top-line summary of major changes in the PLX108-13 clinical study protocol (Version 9.0).

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
1	**Updated dose modification guidelines.** The following sections of the protocol were updated: Section 7.5 (Dose Modification Guidelines)
2	**Updated guidelines for concomitant dosing of CYP3A inducers, CYP3A/UGT inhibitors, hormonal contraceptives, and proton-pump inhibitors.** The following sections of the protocol were updated: Section 7.7.1 (CYP3A inducers) Section 7.7.2 (CYP3A and UGT Inhibitors) Section 7.7.3 (Hormonal Contraceptives) Section 7.7.4 (Acid-reducing Agents) Section 7.8 (Dosage Modification for Renal Impairment)
3	**Updated list of common CYP3A inhibitors and inducers** The following sections of the protocol were updated: ATTACHMENT 2: LIST OF COMMON CYP3A INHIBITORS AND INDUCERS

1.0 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ALT	Alanine aminotransferase
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
AUC_{0-6}	Area Under the concentration-time Curve from time zero to 6 hrs post dosing
AUCinf	Area Under the concentration-time Curve from time zero to infinity
BID	Twice daily
BUN	Blood Urea Nitrogen
Ca++	Calcium
CBC	Complete Blood Count
CFDA	China Food and Drug Administration
CHF	Congestive Heart Failure
Cl-	Chloride
C_{max}	Maximum observed concentration
CR	Complete Response
CRF	Case Report Form
Cr	Creatinine
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CSD	Chronically Sun Damaged
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EIU	Exposure In Utero
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
G-CSF	Granulocyte-Colony Stimulating Factor
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

Abbreviation or Term	Definition/Explanation
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
mm^3	Cubic millimeters
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-Observed-Adverse-Effect Level
NY	New York
OS	Overall Survival
PD	Pharmacodynamic(s) or Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PPI	Proton Pump Inhibitor
PR	Partial Response
PT/INR	Prothrombin Time/International Normalized Ratio
QT	Interval between the start of the Q wave and the end of the T wave
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
RR	Respiratory Rate
SAE	Serious Adverse Event
SD	Stable Disease
T_{max}	Time of maximum observed concentration
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell

2.0 PROTOCOL SYNOPSIS

Title:	Phase I/II Open Label, Multicenter Study of PLX3397 in Patients with Unresectable or Metastatic KIT-mutated Melanoma
Sponsor:	Daiichi Sankyo Co., Ltd.
Clinical Phase:	I/II
Indication(s):	Unresectable stage III or stage IV KIT-mutated melanoma
Objectives:	The objectives of the Pilot portion of the study are: • To evaluate the safety profile of PLX3397 1000 mg per day when administeredtwice daily (BID) orally as a single agent to patients with unresectable or metastatic KIT-mutated melanoma • To determine the pharmacokinetics (PK) of PLX3397 The objectives of the Phase II portion of the study are: • To determine the preliminary efficacy of PLX3397 • To evaluate the safety profile of PLX3397 The exploratory objectives are: • To evaluate the pharmacodynamics as well as the association between KIT mutation type and response to therapy (Pilot and Phase II portions of the study) • To evaluate tumor response by positron emission tomography (PET) scan on Day 1 of Cycle 2 compared to Baseline (Pilot portion and first 13 patients of the Phase II portion of the study)
Study Design:	This Phase I/II, open label, multicenter study includes a dose evaluation portion (Pilot phase) in which the safety profile of PLX3397 as a single oral agent will be evaluated, followed by an expansion cohort (Phase II) in which the efficacy and safety of PLX3397 administered at the recommended Phase II dose (RP2D) will be evaluated in patients with unresectable stage III or stage IV KIT-mutated melanoma. The Pilot portion of the study follows a 3+3 design to determine if 1000 mg per day is the appropriate dose for the Phase II portion. Three patients are planned to be dosed initially. If 0 or 1 of 3 patients at the 1000 mg dose level cohort experience a dose-limiting toxicity (DLT), 3 additional patients will be enrolled for a total of 6 patients. If ≥2 of 6 patients experience a DLT at the 1000 mg per day dose, the dose will be de-escalated to 800 mg per day. If 0 or 1 of 3 patients at the 800 mg per day dose level cohort experiences a DLT, 3 additional patients will be enrolled for a total of 6 patients. If ≥2 of 6 patients experience a DLT at the 800 mg dose, the study will be terminated due to intolerability. Additional patients may be enrolled in a dose cohort based on safety and efficacy observations. The RP2D can be either 1000 mg per day or 800 mg per day based on discussions between the Sponsor and the investigators. The RP2D will be further evaluated in an expansion cohort during the Phase II portion of the study. In the Phase II portion of the study, an analysis of anti-tumor response will be carried out after approximately 13 patients have been treated. If 3 or more responses are seen (complete response (CR) and partial response (PR) based upon Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or PET imaging), an additional approximately 19 patients will be enrolled and treated.
Number of Patients:	Approximately 44 patients are planned for enrollment **Pilot:** Approximately 6-12 patients **Phase II:** Approximately 32 patients
Study Procedures:	Procedures include medical history, physical examination, vital sign assessment, 12-lead electrocardiography (ECG), clinical laboratory evaluations (serum chemistry, hematology, urinalysis), pregnancy testing, and eastern cooperative oncology group (ECOG)

	performance status assessment. Concomitant medications and adverse events (AEs) will be monitored and recorded throughout the study. Radiographic tumor response assessment by computed tomography (CT) scan will be performed every 8 weeks × 3 (at the end of Cycles 2, 4, 6), then every 12 weeks thereafter (e.g., at the end of Cycles 9, 12, 15, and onward). Information on qualified KIT mutation(s) will be collected, and archived tumor tissue will be collected at Screening. Fresh tumor tissue for the purpose of exploratory pharmacodynamics will be obtained at baseline (Day 1) and optionally also at Day 15 of Cycle 1 and End-of-treatment **in the Pilot portion and first 13 patients of the Phase II portion**. PET scan will be obtained at baseline (Day 1) and Day 1 of Cycle 2 in the Pilot portion and first 13 patients of the Phase II portion.
Inclusion/ Exclusion Criteria:	*To be eligible for enrollment, patient must meet <u>all</u> inclusion and exclusion criteria.* **Inclusion Criteria:** 1. Age ≥18 years 2. Unresectable stage III or stage IV melanoma which is histologically confirmed at the treating institution with KIT mutation(s) not known to be resistant to PLX3397 (see Table 9-1). Note: Patients with KIT exon 8, 9, 11, 13, and 14 mutations are the most likely to be sensitive to PLX3397. Patients with KIT exon 17 or 18 mutations D816V, Y823D, and A829P should not be enrolled as they are not sensitive to PLX3397. Other KIT exon 17 or 18 mutations may be sensitive to PLX3397 and should be enrolled. 3. No limit on prior systemic therapies for melanoma. Patients who have not received prior therapy are eligible if they have a potentially sensitive KIT mutation. 4. Presence of measurable lesions by RECIST v1.1 5. ECOG performance status 0, 1, or 2 6. Life expectancy ≥3 months in the judgment of the investigator 7. Adequate organ and bone marrow function a. Absolute neutrophil count (ANC) ≥1.5 X 10^9/L, Hgb ≥10 g/dL, platelet count≥100 X 10^9/L b. AST/ALT ≤2.5 X upper limit of normal (ULN) or <5 X ULN in the presence of liver metastases, total bilirubin ≤1.5 ULN (unless due to Gilbert's Syndrome, in which case it must be ≤2.5 mg/dL), albumin ≥3.0 g/dL c. Serum creatinine ≤1.5 X ULN or calculated creatinine clearance (CrCl) >60 mL/min using the Cockcroft-Gault formula Patients may be transfused or receive granulocyte-colony stimulating factor (G-CSF) or growth factors. 8. Women of child-bearing potential must have a negative serum pregnancy test at Screening and must agree to use an effective form of contraception from the time of the negative pregnancy test up to 3 months after the last dose of study drug. Effective forms of contraception include abstinence, hormonal contraceptive (injectable or implantable) in conjunction with a barrier method, or a double barrier method. Women of non-child-bearing potential must have been postmenopausal for ≥1 year or surgically sterile. 9. Fertile men must agree to use an effective method of birth control during the study and for up to 3 months after the last dose of study drug. 10. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements **Exclusion Criteria:** 1. Prior treatment with a KIT inhibitor for melanoma 2. Known presence of NRAS or BRAF mutation

	3. Exposure to any chemotherapy, antibody or antibody drug conjugate, small molecule TKI, immunotherapy (e.g., PD-1, PD-L1, or CTLA-4 inhibitors – either antibody or small molecule), investigational drug, or radiation therapy within 28 days prior to Cycle 1 Day 1 (C1D1). 4. Unresolved Grade >1 clinically significant (in the judgment of the investigator) adverse effects from previous therapy prior to C1D1 5. Symptomatic brain metastases. Subjects with untreated brain metastasis ≤1 cm can be considered eligible if deemed asymptomatic by the investigator upon consultation with the medical monitor and do not require immediate radiation or steroids. Subjects with brain metastasis that is treated and stable for 1 month may be considered eligible if they are asymptomatic and on stable dose of steroids or if they do not require steroids following successful local therapy. 6. History of another malignancy (within 2 years prior to first study drug administration) unless malignancy was treated with curative intent and likelihood of relapse is small (<5% in 2 years in the judgment of the investigator). Patients with a history of squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix may be enrolled. 7. Concomitant treatment with other anti-neoplastic agents (hormonal therapy acceptable) 8. Uncontrolled intercurrent or infectious illness 9. Major surgical procedure or significant traumatic injury within 14 days of initiating study drug or anticipation of the need for major surgery during the study 10. Previous radiotherapy to 25% or more of the bone marrow and/or radiation therapy within 28 days prior to C1D1 11. Inability to swallow capsules, or refractory nausea and vomiting, malabsorption, an external biliary shunt, or significant bowel resection that would preclude adequate absorption 12. Congestive heart failure (CHF) New York (NY) Heart Association class III or IV; unstable coronary artery disease (myocardial infarction [MI] more than 6 months prior to study entry is permitted); or serious cardiac arrhythmia 13. Baseline QTcF ≥450 ms (males) or ≥470 ms (females) 14. Known active or chronic infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV). Active or chronic HBV infection is defined as being hepatitis B surface antigen (HBsAg) or HBV DNA-positive. Chronic HCV is defined as being anti-HCV or HCV RNA-positive 15. Known chronic liver disease 16. Women who are breast-feeding or pregnant
Duration of Study:	**Screening Period:** 28 days **Treatment Period:** Subjects will receive study drug twice daily during each 28-day cycle. There is no limit to the number of treatment cycles that can be administered. The treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or a protocol violation. Subjects receiving clinical benefit from treatment (stable disease or better) will be offered the opportunity to continue therapy with pexidartinib in the extension phase of this protocol. **Follow-up Period:** All patients will undergo an End-of-Study evaluation within 28 days of the last dose of study drug and prior to the initiation of any new anti-cancer therapy (if applicable). Thereafter, patients will be contacted by phone every 3 months during year 1 and every 6 months thereafter to obtain information about subsequent treatment(s) and survival status.
Test Product, Dose, and	PLX3397 will be supplied in 200 mg capsules and will be taken BID approximately 12 hours apart. Each dose is to be taken with approximately 200 mL of water. Subject will fast

Mode of Administration:	for at least one hour before and one hour after dosage. Each cycle of treatment will last 28 days. During the Pilot portion of the study, 3 to 6 patients in sequential dose cohorts will be enrolled. The dose cohorts are as follows: • Cohort 1: 1000 mg/day (400 mg in the morning and 600 mg in the evening) • Cohort -1 (if required): 800 mg/day (400 mg BID) Cohort -1 will be carried out only if Cohort 1 is considered intolerable. Study treatment may be delayed up to 2 weeks to permit resolution of any treatment-related toxicity outside the DLT window. The dose level for the Phase II portion of the study will be the RP2D as determined from the Pilot phase. Study drug will be administered BID in a fasting state.
Definition of Dose-limiting Toxicity (DLT):	A DLT is defined as an AE assessed as being possibly or probably related to study drug administration that is: • Not due to the underlying malignancy; • Has no clear evidence of an alternative etiology; and • Meets one of the following CTCAE v. 4.03 criteria during the first 28 days of PLX3397 administration: Any Grade ≥3 clinically significant hematologic toxicity except: Grade 3 lymphopenia Grade 3 neutropenia ≤7 days Any thrombocytopenia resulting in clinically significant bleeding Any Grade ≥3 clinically significant non-hematologic toxicity except: Nausea, vomiting, and/or diarrhea of Grade 3 severity that resolves to Grade ≤2 within 7 days with optimal prophylaxis and/or treatment. Grade 3 fatigue that resolves to Grade ≤2 within 7 days. Grade ≥3 alkaline phosphatase that is related to underlying malignancy (e.g., bone metastasis) If, for any reason, either the Sponsor or principal investigator deems further dose reduction inappropriate. Final decisions on determination of DLTs will be made in consultation between the Sponsor and the principal investigator. Any dose reduction required during Cycle 1 due to potential toxicity. For the purposes of determining the DLT in Cycle 1, the use of G-CSF or other hematologic growth factors is not permitted during Cycle 1. If a patient develops a protocol defined hematologic DLT and requires the use of G-CSF or other hematologic growth factors, they may be used in accordance with local standard of care, and per Section 7.7.
Stopping Rules:	**Pilot portion:** • If ≥2 of 6 patients experience DLTs in cohort 1 (1000 mg/day), Cohort -1 (800 mg per day) will be activated • If ≥2 of 6 patients in Cohort -1 experience DLTs, the study will be terminated due to intolerability. **Phase II:** • Subjects will be discontinued from the study for reasons of disease progression, unacceptable toxicity, consent withdrawal, a protocol violation, or noncompliance (taking less than 80% of study drug). Noncompliant patients may be replaced. Patients will be discontinued from the study if they are off study drug for more than 2 weeks, regardless of the reason, unless the patient has demonstrated a clinical benefit from therapy and would like to continue dosing with study drug after discussion between the investigator and the Sponsor.

	The Pilot and Phase II portions of the study may be discontinued if the study is terminated by the Sponsor, the China Food and Drug Administration (CFDA), or other regulatory authorities.
Safety and Tolerability Assessments:	Physical examination, vital signs, 12-lead ECG, AEs, and clinical laboratory evaluations (hematology, serum chemistry, urinalysis).
PK Parameters:	The pharmacokinetic profile of plasma PLX3397 will be analyzed by measuring area under the plasma concentration–time curve (AUC_{0-6}), peak concentration (C_{max}), and time of maximum observed concentration (T_{max}).
PD Parameters:	Histological/molecular analysis of paired fresh tumor biopsy, and PET scan evaluation on Day 1 of Cycle 2 compared to Baseline in the Pilot portion and the first 13 patients in the Phase II portion of the study will be performed. Exploratory tissue studies will include immunohistochemistry (IHC) for KIT, pERK, Ki67 and other markers of target or tumor evaluation. Other exploratory evaluations may include assessment of the tumor microenvironment by IHC or other methods for immune cell expression/number (e.g., PD-1). Exploratory blood studies will measure CSF-1 and circulating tumor DNA (ctDNA) (Phase II portion in Korea Only).
Endpoints:	<u>The endpoints in the Pilot portion of the study include:</u> • DLTs will define the RP2D (1000 mg per day or 800 mg per day) • Safety endpoints (i.e., AEs, clinical laboratory evaluations, ECGs, physical examinations, and vital sign measurements) • PK analysis • Serum/plasma tumor biomarkers including CSF-1 <u>The exploratory endpoints in the Pilot portion of the study include:</u> • IHC and molecular analysis of archival and paired fresh tumor biopsy • PET scan evaluation on Day 1 of Cycle 2 compared to Baseline <u>The primary endpoint in the Phase II portion of the study includes:</u> • Objective response rate (ORR), which is the sum of CR and PR by RECIST v1.1 <u>The secondary endpoints in the Phase II portion of the study include:</u> • Duration of response (DoR) • Progression free survival (PFS) • Overall survival (OS) • Safety endpoints (i.e., AEs, clinical laboratory evaluations, ECGs, physical examinations, and vital sign measurements) <u>The exploratory endpoints in the Phase II portion of the study include :</u> • IHC and molecular analysis of archival and paired fresh tumor biopsy • Serum/plasma tumor biomarkers including CSF-1. • ctDNA • PET scan evaluation on Day 1 of Cycle 2 compared to Baseline
Statistical Considerations	The Phase II portion of the study will follow a Simon two-stage design to compare a null ORR of 15% with an alternative ORR of 40% with 90% power and a one-sided type I error of 5%. With the assumption of 10% drop-out, the total sample size will be 32 patients to achieve 29 evaluable patients. Thirteen patients will be enrolled in the first stage, with at least three responses required to proceed to the second stage. Eight responses among 29 evaluable patients are required for PLX3397 to be considered promising.

Table 2-1: Schedule of Events for Pilot Portion of Study

	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent Cycles[2]	Extension phase[21] (every 28 days)	End of Study[3]	Post-Study Follow-up[4]
Procedure	**Day –28 to –1[1]**	**Day 1**	**Day 8 ± 3d**	**Day15 ± 3d**	**Day 22 ± 3d**	**Day 1 ± 3d**	**Day 8 ± 3d[17]**	**Day 15 ± 3d**	**Day 22 ± 3d[17]**	**Day 1 ± 3d**	**Day 1 ± 3d**		
Consent	X												
Medical history	X												
Archival Tissue[15]	X												
KIT mutation documentation[5]	X												
Physical examination[6], vital signs	X	X[18]		X		X		X		X	X	X	
Height	X												
Weight	X											X	
ECOG Performance Status	X	X[18]		X		X		X		X		X	
ECG[7]	X			X		X						X	
Hematology[8]	X	X[18]	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[20]	X	X[18]	X	X	X	X	X	X	X	X	X	X	
Urinalysis[8]	X	X[18]				X				X			
Coagulation Profile (PT/INR)[8]	X												
Serum pregnancy test[9]	X												
Blood sampling for PK[10]		X		X									
Blood sampling for PD[16]		X		X									
In-clinic study drug administration (am dose)		X		X									
Adverse events	X	X	X	X	X	X		X		X	X	X	
Concomitant medications[11]	X	X	X	X	X	X		X		X		X	
Study drug compliance[19]				X		X		X		X	X		
CT chest, abdomen, pelvis[12]	X									X [12]	X[22]		
PET scan[13]		X				X							
Fresh tumor biopsy[14]		X		X								X	
Phone interview													X

1. Protocol-specified screening procedures that are performed as part of standard of care and within 28 days of Day 1 of Cycle 1 may be used for screening purposes. Clinical laboratory studies and baseline CT scan must be performed within the 14-day period before Day 1 of Cycle 1.
2. If the study treatment is well tolerated and the patient experiences no disease progression, then the clinic visit, laboratory studies and other procedures indicated in the column (except CT chest/abdomen/pelvis – see footnote 11) will be performed every 4 weeks at the beginning of each cycle.
3. The End-of-Study visit should be scheduled within the 28-day period after the last dose of study drug and before starting any new anti-neoplastic therapy.
4. A post-study follow-up contact by phone by site staff will be conducted every 3 months during Year 1, then every 6 months thereafter to obtain information on any new anti-cancer therapy received and survival status.
5. Documentation of KIT mutation(s) prior to enrollment to include submission of deidentified sequencing report and associated .scf, .ab1, or equivalent output files.
6. A complete physical examination will be performed at screening. All subsequent physical examinations will be disease-specific.
7. ECG will be performed after the patient has been in a supine position for at least 5 minutes. It will be performed at Screening, before and 2 hours (± 30 minutes) after the morning dose on Day 15 of Cycle 1, Day 1 of Cycle 2, and at the End-of-Study visit.
8. A complete blood count (CBC) with a differential count and comprehensive chemistry will be performed every 7 days during Cycle 1, Cycle 2, at the beginning of each cycle starting with Cycle 3 and onward, and at the end of the study. Urinalysis will be performed at Screening and at the beginning of each cycle. PT/INR will be performed at Screening.
9. For women of child-bearing potential, a screening serum pregnancy test must be negative within 7 days of Day 1 of Cycle 1.
10. On Day 1 and Day 15 of Cycle 1 during the Pilot portion of the study, blood samples for pharmacokinetic (PK) analysis will be obtained pre-morning dose, and 0.5, 1, 2, 4, and 6 hours post-morning dose (± 10 minutes at the 0.5- and 1-hour post-dose timepoints, and ± 30 minutes at the 2-, 4-, and 6-hour post-dose timepoints).
11. Concomitant medications will include non-prescribed medications and any complementary/herbal supplements.
12. CT with and without contrast to assess tumor status will be performed every 8 weeks during the first 24 weeks of study treatment, then every 12 weeks thereafter (e.g., at the end of Cycles 2, 4, 6, then at the end of Cycles 9, 12, 15 and onward). PET/CT scan may be used as well.
13. PET scan will be performed at Day 1 (-3d) of Cycle 1 or before fresh tumor biopsy in screening and Day 1 (± 3d) of Cycle 2 for patients enrolled in the Pilot portion of the study. If a PET/CT scan is performed, then no additional PET scan is needed.
14. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (±3d) (optional), and at the End-of-Study visit (optional) for subjects enrolled in the Pilot portion of the study. Biopsies must be core needle or excisional (not fine needle), and sufficient for 20 unstained slides of 5 micron thickness. If a Screening tumor biopsy was obtained (Day -28 to Day -1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required. All PET scans should be performed prior to biopsy collection procedures to avoid false positive results.
15. Availability of archival tissue should be documented and at least 10 unstained slides of 5 micron thickness should be submitted to the central lab.
16. On Day 1 and Day 15 of Cycle 1 during the Pilot portion of the study, blood samples for pharmacodynamics (PD) analysis will be obtained pre-morning dose.
17. Assessments on these visits may be performed at a local hospital or testing facility for patient convenience. Results should be shared with the Principal Investigator within 48 hours.
18. ECOG Performance Status, symptom-directed physical examination, hematology, serum chemistry, and urinalysis do not need to be repeated if these assessments from Screening occurred within 3 days of C1D1 unless a change in status is suspected.
19. Drug Diary to be reviewed. Collection of completed drug diary and distribution of new diary to occur at beginning of each cycle.
20. Serum chemistry could be more frequent if liver function test are elevated and reference the dose modification (Section 7.5).
21. Subjects receiving clinical benefit from study treatment at the time of data cut-off, will be offered the opportunity to continue pexidartinib treatment in an extension phase. Subjects will continue until disease progression, unacceptable toxicity, or withdrawal of consent.
22. CT with and without contrast to assess tumor status will be performed every 12 weeks. PET/CT scan may be used as well.

Table 2-2: Schedule of Events for Phase II Portion of Study

Procedure	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent Cycles [2]	End of Study[3]	Post-Study Follow-up[4]
	Day –28 to –1[1]	Day 1	Day 8 ± 3d	Day15 ± 3d	Day 22 ± 3d	Day 1 ± 3d	Day 8 ± 3d[16]	Day 15 ± 3d	Day 22 ± 3d[16]	Day 1 ± 3d		
Consent	X											
Medical history	X											
Archival Tissue[14]	X											
KIT mutation documentation[5]	X											
Physical examination[6], vital signs	X	X[17]		X		X		X		X	X	
Height	X											
Weight	X										X	
ECOG Performance Status	X	X[17]		X		X		X		X	X	
ECG[7]	X			X		X					X	
Hematology[8]	X	X[17]	X	X	X	X	X	X	X	X	X	
Serum chemistry[20]	X	X[17]	X	X	X	X	X	X	X	X	X	
Urinalysis[8]	X	X[17]				X				X		
Coagulation Profile (PT/INR)[8]	X											
Serum pregnancy test[9]	X											
Blood sampling for PD[10]		X		X								
In-clinic study drug administration (am dose)		X		X								
Adverse events	X	X	X	X	X	X		X		X	X	
Concomitant medications[11]	X	X	X	X	X	X		X		X	X	
Study drug compliance[18]				X		X		X		X		
CT chest, abdomen, pelvis[12]	X									X [12]		
PET scan[15]		X				X						
Fresh tumor biopsy[13]		X		X							X	

Procedure	Screening	Cycle 1				Cycle 2				Cycle 3 and Subsequent Cycles [2]	End of Study[3]	Post-Study Follow-up[4]
	Day –28 to –1[1]	Day 1	Day 8 ± 3d	Day15 ± 3d	Day 22 ± 3d	Day 1 ± 3d	Day 8 ± 3d[16]	Day 15 ± 3d	Day 22 ± 3d[16]	Day 1 ± 3d		
Circulating tumor DNA (ctDNA)[19] (Korea sites only)		X				X				X	X	
Phone interview												X

1. Protocol-specified screening procedures that are performed as part of standard of care and within 28 days of Day 1 of Cycle 1 may be used for screening purposes. Clinical laboratory studies and baseline CT scan must be performed within the 14-day period before Day 1 of Cycle 1.
2. If the study treatment is well tolerated and the patient experiences no disease progression, then the clinic visit, laboratory studies and other procedures indicated in the column (except CT chest/abdomen/pelvis – see footnote 11) will be performed every 4 weeks at the beginning of each cycle.
3. The End-of-Study visit should be scheduled within the 28-day period after the last dose of study drug and before starting any new anti-neoplastic therapy.
4. A post-study follow-up contact by phone by site staff will be conducted every 3 months during Year 1, then every 6 months thereafter to obtain information on any new anti-cancer therapy received and survival status.
5. Documentation of KIT mutation(s) prior to enrollment to include submission of deidentified sequencing report and associated .scf, .ab1, or equivalent output files.
6. A complete physical examination will be performed at screening. All subsequent physical examinations will be disease-specific.
7. ECG will be performed after the patient has been in a supine position for at least 5 minutes. It will be performed at Screening, before and 2 hours (± 30 minutes) after the morning dose on Day 15 of Cycle 1, Day 1 of Cycle 2, and at the End-of-Study visit.
8. CBC with a differential count and comprehensive chemistry will be performed every 7 days during Cycle 1, Cycle 2, at the beginning of each cycle starting with Cycle 3 and onward, and at the end of the study. Urinalysis will be performed at Screening and at the beginning of each cycle. PT/INR will be performed at Screening.
9. For women of child-bearing potential, a screening serum pregnancy test must be negative within 7 days of Day 1 of Cycle 1.
10. On Day 1 and Day 15 of Cycle 1 during the Phase II portion of the study, blood samples for pharmacodynamics (PD) analysis will be obtained pre-morning dose.
11. Concomitant medications will include non-prescribed medications and any complementary/herbal supplements.
12. CT with and without contrast to assess tumor status will be performed every 8 weeks during the first 24 weeks of study treatment, then every 12 weeks thereafter (e.g., at the end of Cycles 2, 4, 6, then at the end of Cycles 9, 12, 15 and onward). PET/CT scan may be used as well.
13. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (-3d) (optional), and at the End-of-Study visit (optional) for first 13 patients enrolled in Phase II. Biopsies must be core needle or excisional (not fine needle), and sufficient for 20 unstained slides of 5 micron thickness. If a Screening tumor biopsy was obtained (Day −28 to Day −1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required. All PET scans should be performed prior to biopsy collection procedures to avoid false positive results.
14. Availability of archival tissue should be documented and at least 10 unstained slides of 5 micron thickness should be submitted to the central lab.
15. PET scan will be performed at Day 1 (-3d) of Cycle 1 or before fresh tumor biopsy in screening and Day 1 (± 3d) of Cycle 2 for the first 13 patients enrolled in the Phase II portion of the study. If a PET/CT scan is performed, then no additional PET scan is needed.
16. Assessments on these visits may be performed at a local hospital or testing facility for patient convenience. Results should be shared with the Principal Investigator within 48 hours.

17. ECOG Performance Status, symptom-directed physical examination, hematology, serum chemistry, and urinalysis do not need to be repeated if these assessments from Screening occurred within 3 days of C1D1 unless a change in status is suspected.
18. Drug Diary to be reviewed. Collection of completed drug diary and distribution of new diary to occur at beginning of each cycle.
19. Korea sites only. Whole blood for circulating tumor DNA assessment to be done pre-dose and the End of Study visit.
20. It could be more frequent if liver function test are elevated and reference the dose modification (Section 7.5).

3.0 BACKGROUND AND STUDY RATIONALE

3.1. Background

The incidence of malignant melanoma continues to increase globally, and this includes Asia. Up to the end of 2010, the incidence of melanoma in Beijing, China was 8.9 per 100000 people (Si 2013). Melanomas can be generally classified into 4 subtypes: (1) melanomas that occur on skin without chronic sun-induced damage (non-CSD); (2) melanomas on skin with chronic sun-induced damage (CSD); (3) mucosal melanomas, and (4) acral melanomas. The incidence of these 4 subtypes differs significantly among different races and ethnicities (Kong 2011). In the Chinese and other Asian populations, acral and mucosal melanomas are the predominant subtypes, accounting for approximately 65% of all melanomas (Chi 2011). Five-year survival rates of Chinese patients with stage I, II, III, and IV diseases were 94.1%, 44.0%, 38.4%, and 4.6%, respectively (Chi 2011).

In a large analysis which comprised 502 samples from melanoma patients screened for KIT mutations at Peking Cancer Hospital & Institute, the overall mutation frequency was 10.8% (54/502), with the highest mutation frequency within the CSD subgroup (20.7%); in the acral and mucosal melanoma subtypes, the frequency of KIT mutations was 11.9% (23/193) and 9.6% (16/167), respectively. Importantly, the overall survival of melanoma patients with KIT mutations was significantly shorter than that of patients without such alterations ($p = 0.001$) (Kong 2011).

Until recently, there had been no improvements in outcome for patients with advanced disease for several decades. The identification of an activating mutation in BRAF in 50% of melanoma patients (Davies 2002) led to the development of vemurafenib, a highly active targeted therapy that benefits approximately 80% of eligible patients, is associated with a significant survival benefit, and is now a standard of care in advanced disease (Chapman 2011). Apart from BRAF, KIT is the only other aberrant signaling molecule for which targeted drugs are available. Some evidence of efficacy for imatinib in KIT advanced melanoma has been reported in two Phase II trials (Guo 2011). However, KIT mutations are heterogeneous, and many do not respond to imatinib therapy (Si 2013; Carvajal 2011). To date, there has been no therapy approved for KIT mutated melanoma.

PLX3397 is a novel, orally active, small molecule inhibitor that targets a variety of KIT mutations, as well as CSF1R (Fms), and oncogenic Flt3, but remains highly selective versus other kinases. Few preclinical models for Kit-mutant melanoma exist, but preliminary results from an ongoing study of PLX3397 in one model are promising. This model is based on a patient-derived tumor xenograft from a patient with sinal-nasal melanoma. This patient had been treated with the kinase inhibitor nilotinib and experienced partial tumor regression at 3 months. After 6 months a new subcutaneous lesion appeared and a biopsy of this lesion was removed and propagated in immunocompromised mice. Tumors in these mice grew to 100 mm^3 in 12 days and treatment with PLX3397 (chow formulation, nominal strength of 46 mg/kg) was initiated. As shown in Figure 3-1 below, vehicle-treated animals (n = 12) were sacrificed at Week 7, while PLX3397 treatment resulted in tumor regression (n = 12). PLX3397 treatment was stopped at Week 13, and three of the 12 animals showed re-growth of the tumor.

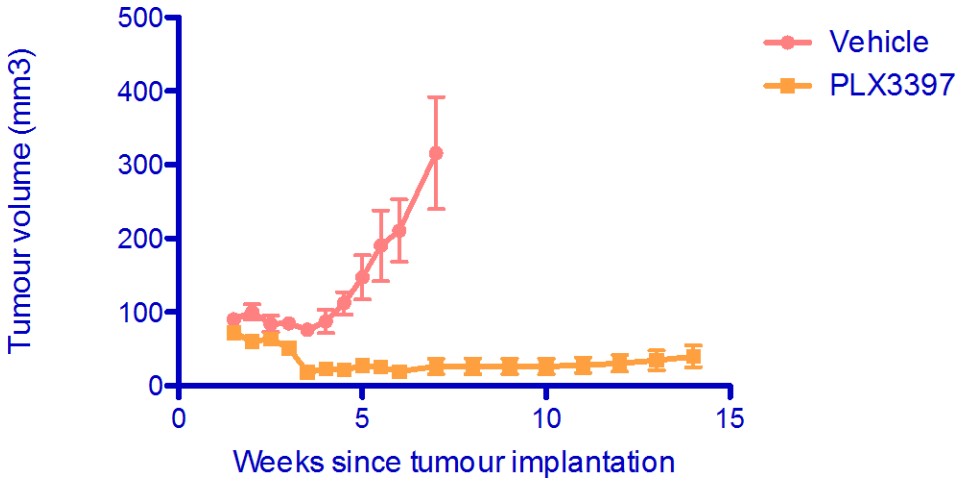

Figure 3-1: PLX3397 Causes Tumor Regression in a Patient-Derived Xenograft Model of Kit-Mutant Melanoma

It is now widely accepted that tumor-associated macrophages (TAMs) play a critical role in promoting tumor angiogenesis, metastasis and creating an immunosuppressive microenviroment for tumor growth (Hao 2012). PLX3397 targets these TAMs by blocking the Fms receptor on their surface. Pharmacology models show that PLX3397 blocks Fms activity in vivo, and significantly reduces the incidence of lymph node metastasis in the A2058 BRAF-mutant xenograft model. In addition, synergistic efficacy is demonstrated when PLX3397 is combined with BRAF inhibition in this same model, providing a possible explanation for the beneficial effect of FMS blockade in the tumor microenviroment. See the PLX3397 Investigator's Brochure for further details.

3.1.1. Nonclinical Experience

Good Laboratory Practice (GLP) safety pharmacology studies (in vitro hERG, dog cardiovascular, rat central nervous system, and rat respiratory) did not identify any meaningful test article related effects.

In the GLP 13-week rat oral gavage study at doses of 0.5, 4 and 20 mg/kg/day, there were no test article-related clinical observations or effects on body weights, food consumption, ophthalmic examinations, urinalysis, or macroscopic examinations. Systemic toxicity was observed at a dosage level of 20 mg/kg/day, as evidenced by anemia and mild to moderate generalized bone marrow depletion in both sexes, and minimal to moderate hepatocellular vacuolation associated with higher AST, ALT, and cholesterol values in males. The no-observed-adverse-effect level (NOAEL) was considered to be 4 mg/kg/day.

In the GLP 13-week dog oral gavage study at doses of 1, 6, and 30 mg/kg/day, there were no test article-related macroscopic findings. Body weights, food consumption, ophthalmic, and electrocardiography parameters were unaffected by test article administration. Systemic toxicity was observed at the dosage level of 30 mg/kg/day, as evidenced by microscopic findings of generalized depletion of all germ cell populations in the testes, moderate hypospermatogenesis,

and moderate or severe hypospermia in the epididymides, which were consistent with observed lower absolute and relative testes weights and lower testicular volume in this group and sex. The NOAEL was considered to be 6 mg/kg/day for males.

In GLP genotoxicity studies (Ames, chromosomal aberrations, and mouse bone marrow micronucleus), there was no evidence of mutagenic or clastogenic effects.

See the PLX3397 Investigator's Brochure for further details.

3.1.2. Clinical Experience

PLX3397 is being evaluated in both solid tumors and hematological malignancies. Approximately 345 patients have been exposed to PLX3397 doses ranging from 200 mg/day to 5000 mg/day for up to 16 months. The recommended Phase II dose (RP2D) for solid tumors is 1000 mg/day, and the RP2D for patients with Flt3-ITD AML (acute myelogenous leukemia) is 3000 mg/day.

No safety signals in vital signs, physical examinations, or electrocardiograms (ECGs) (including careful evaluation of potential electrocardiogram Interval between the start of the Q wave and the end of the T wave (QT) prolongation) have been identified. At doses of ≥600 mg/day, transient and reversible increases in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) have been observed in approximately half of the patients. In addition, 1 case of liver enzyme elevation in association with an elevated bilirubin which was considered possibly drug-related was noted in study PLX108-04 (Phase II, single agent study in subjects with glioblastoma multiforme). Transient increases in AST and ALT were seen in the 13-week rat study, but not in the dog study. In addition to increased AST among solid tumor patients, the most common adverse events (AEs) have been fatigue, decreased appetite, nausea, vomiting, anemia, hair color change (depigmentation), and diarrhea.

Details on the clinical experience with PLX3397 can be found in the Investigator's Brochure.

3.2. Rationale for Dose Selection and Study Design

As summarized above (and discussed in detail in the Investigator's Brochure), the safety of PLX3397 has been evaluated in patients with a range of tumor types, including solid tumors, hematologic malignancy, and in combination with chemotherapeutic agents. The selection of 1000 mg per day as the initial dose to be evaluated in the Pilot portion of this study was based upon the safety data from PLX108-01, a dose-escalation study of PLX3397 in solid tumor patients followed by expansion cohorts of patients receiving PLX3397 at the RP2D. In the dose escalation portion of the study, 1000 mg per day was identified as the RP2D, and the safety of 1000 mg per day was further evaluated in over 75 additional solid tumor patients. As this is the first time PLX3397 will be studied in melanoma patients, a Pilot portion of the study will confirm the safety and tolerability of 1000 mg per day in this patient population. A dose de-escalation option will allow dose reduction to 800 mg per day in the event that 1000 mg per day is not well tolerated. Doses below 800 mg per day are anticipated to result in reduced efficacy and will not be considered in this study.

Once the RP2D is selected from the Pilot portion, the study will be expanded to include an additional 32 patients to evaluate the anti-tumor activity of PLX3397 in KIT-mutated melanoma. The Phase II portion of this study will enroll patients in two stages. Thirteen patients will be enrolled in the first stage, with at least three responses (23%) required to proceed to the second stage. With the assumption of 10% drop-out, the total sample size will be 32 patients to achieve 29 evaluable patients. Eight responses (28%) among 29 evaluable patients are required for PLX3397 to be considered promising. In view of the fact that there is no effective and approved therapy for advanced KIT mutated melanoma, a response rate of >40% is considered worthy of further study.

This study design will allow the step-wise evaluation of PLX3397 in patients with advanced KIT-mutated melanoma, with the Pilot portion evaluating the safety of the proposed RP2D of 1000 mg per day and the Phase II Portion providing for an initial evaluation of efficacy (among the first 13 enrolled patients) prior to further enrollment of the full cohort.

The Extension part of the study will allow subjects to continue pexidartinib treatment who demonstrate clinical benefit (SD, PR, or CR). The benefits of transitioning subjects into the extension part are to allow subjects to continue receiving the study drug and monitor for safety, but decrease the amount of procedures.

3.3. Potential Risks and Benefits

The safety of pexidartinib has been evaluated in subjects with a range of tumor types, including solid tumors, hematologic malignancy, and in combination with chemotherapeutic agents. The selection of 1000 mg per day as the initial dose to be evaluated in the several studies was based upon the safety data from Study PLX108-01 and the safety of 1000 mg per day was further evaluated in several clinical studies.

In the GLP repeat-dose toxicology studies consisting of up to 13 weeks of pexidartinib dosing, test article-related AEs were noted in testes (testicular spermatogonia reduction), ovaries (ovarian follicular degeneration), liver, bone and bone marrow, hematology, and lymphoid changes; these changes are consistent with the pharmacological mechanism of action of pexidartinib. All test article-related findings were partially or fully reversible. Potential dose-related changes in bone marrow function can be monitored by peripheral blood cell count and differential counts. Because of the effects on reproductive organs, subjects will be monitored for changes in luteinizing hormone, follicle stimulating hormone, and other sex-specific hormone levels.

Effects on embryo fetal development have been observed in both rat and rabbit toxicology studies. Subjects in the study will be required to use adequate birth control during the study and for 90 days after the last dose of study drug administered.

Findings in the nonclinical canine safety pharmacology study suggest that pexidartinib may have a negative inotropic effect. Subjects will be monitored for changes in ejection fraction with cardiac echocardiograms.

In the clinical evaluation to date, among solid tumor patients, the most common AEs (occurring in ⩾20% of all patients treated with pexidartinib) observed have been fatigue, nausea, decreased

appetite, hair color change (depigmentation), vomiting, diarrhea, headache, and anemia. In the AML study, the most common AEs reported have been diarrhea, nausea, fatigue, febrile neutropenia, vomiting, decreased appetite, anemia, cough, hypokalemia, and increases in AST. In some instances, the increase in liver enzymes may require dose hold or modification. Dosing modification guidance is included within the protocol for AE monitoring. Liver function (serum chemistry), renal function (serum chemistry), and heart electrophysiology (QT interval corrected for heart rate [QTc] evaluation) will be monitored during this study.

Based on the treatment emergent adverse event (TEAE) reports of increased INR observed in patients receiving concomitant warfarin, careful monitoring is required during treatment with pexidartinib. Warfarin doses should be adjusted if an increase in INR is noted.

Updated hepatic safety risk information as of December 2017; please consult the IB for more information: Hepatotoxicity is an important adverse drug reaction. Elevations of liver transaminases and bilirubin have been observed in studies with pexidartinib, together with cases of drug induced cholestasis. Cases of cholestasis have been observed in the first 8 weeks, have generally resolved with treatment discontinuation, but in some cases have been severe, with a protracted course requiring liver dialysis and, in 1 case, transplantation. Hepatotoxicity may be fatal. One fatal case with ongoing cholestatic liver injury at the time of death has been reported. Monitor patients closely as defined in the protocol. Protocol defined dose reductions and discontinuations of pexidartinib, increased frequency of laboratory monitoring, and reporting of findings should be followed (refer to Section 7.5). In addition, rechallenge with pexidartinib should not be attempted without prior discussion with the Sponsor's Medical Monitor.

Pexidartinib is a novel, orally active, small molecule inhibitor that targets CSF1R, Kit, and oncogenic Flt3, but remains highly selective versus other kinases. The potent inhibition of these 3 kinases can be exploited to attack tumors via multiple mechanisms. Pexidartinib has shown a potent inhibitor of the proliferation of these target dependent models.

4.0 STUDY OBJECTIVES

4.1. Pilot Portion Objectives

The objectives of the Pilot portion of the study are:

- To evaluate the safety profile of PLX3397 1000 mg per day when administered twice daily (BID) orally as a single agent to patients with unresectable or metastatic KIT-mutated melanoma
- To determine the pharmacokinetics of PLX3397

4.2. Phase II Objectives

The objectives of the Phase II portion of the study are:

- To determine the preliminary efficacy of PLX3397
- To evaluate the safety profile of PLX3397

4.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate the pharmacodynamics as well as the association between KIT mutation type and response to therapy (Pilot and Phase II portions of the study)
- To evaluate tumor response by positron emission tomography (PET) scan on Day 1 of Cycle 2 compared to Baseline (Pilot portion and first 13 patients of the Phase II portion of the study).

5.0 STUDY DESIGN

5.1. Overview of Study Design

This Phase I/II, open label, multicenter study includes a dose evaluation portion (Pilot phase) in which the safety profile of PLX3397 as a single oral agent will be evaluated, followed by an expansion cohort (Phase II) in which the efficacy and safety of PLX3397 administered at the RP2D will be evaluated in patients with unresectable stage III or stage IV KIT-mutated melanoma (comprising mainly acral, mucosal or CSD forms of the disease).

The Pilot portion of the study follows a 3+3 design to determine if 1000 mg per day is an appropriate dose for the Phase II portion. Three patients are planned to be dosed initially. If 0 or

1 of 3 patients at the 1000 mg dose level cohort experience dose-limiting toxicity (DLT), 3 additional patients will be enrolled for a total of 6 patients. If ≥2 of 6 patients experience DLT at the 1000 mg dose, the dose will be de-escalated to 800 mg per day. If 0 or 1 of 3 patients at the 800 mg dose level cohort experiences DLT, 3 additional patients will be enrolled for a total of 6 patients. If ≥2 of 6 patients experience DLT at the 800 mg dose, the study will be terminated due to intolerability. Additional patients may be enrolled in a dose cohort based on safety and efficacy observations. The RP2D can be either 1000 mg per day or 800 mg per day based on discussions between the Sponsor and the investigators. The RP2D will be further evaluated in an expansion cohort during the Phase II portion of the study.

In the Phase II portion of the study, an analysis of anti-tumor response will be carried out after approximately 13 patients have been treated. If 3 or more responses (23%) are seen (complete response (CR) and partial response (PR) based upon Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or PET imaging), an additional approximately 19 patients will be enrolled and treated.

As of June 30 2018, 6 patients were enrolled in the Pilot portion of the study and received 1000 mg per day dose. Two subjects are currently ongoing. Following a preliminary safety and efficacy assessment of these 6 patients, the sponsor decided to discontinue this study. The sponsor informed the 2 remaining subjects of study discontinuation and re-consented the subjects to continue in the extension part of the study.

It is anticipated that a cut-off date will be established and that the data for the safety variables are considered to be mature. Subjects who benefit from therapy (stable disease or better) and remain on treatment without tumor progression at the time of cut-off will be allowed to continue treatment in an extension part of this study. Treatment will continue until disease progression, unacceptable toxicity, or consent withdrawal.

A graphic overview of the study design is presented in Figure 5-1.

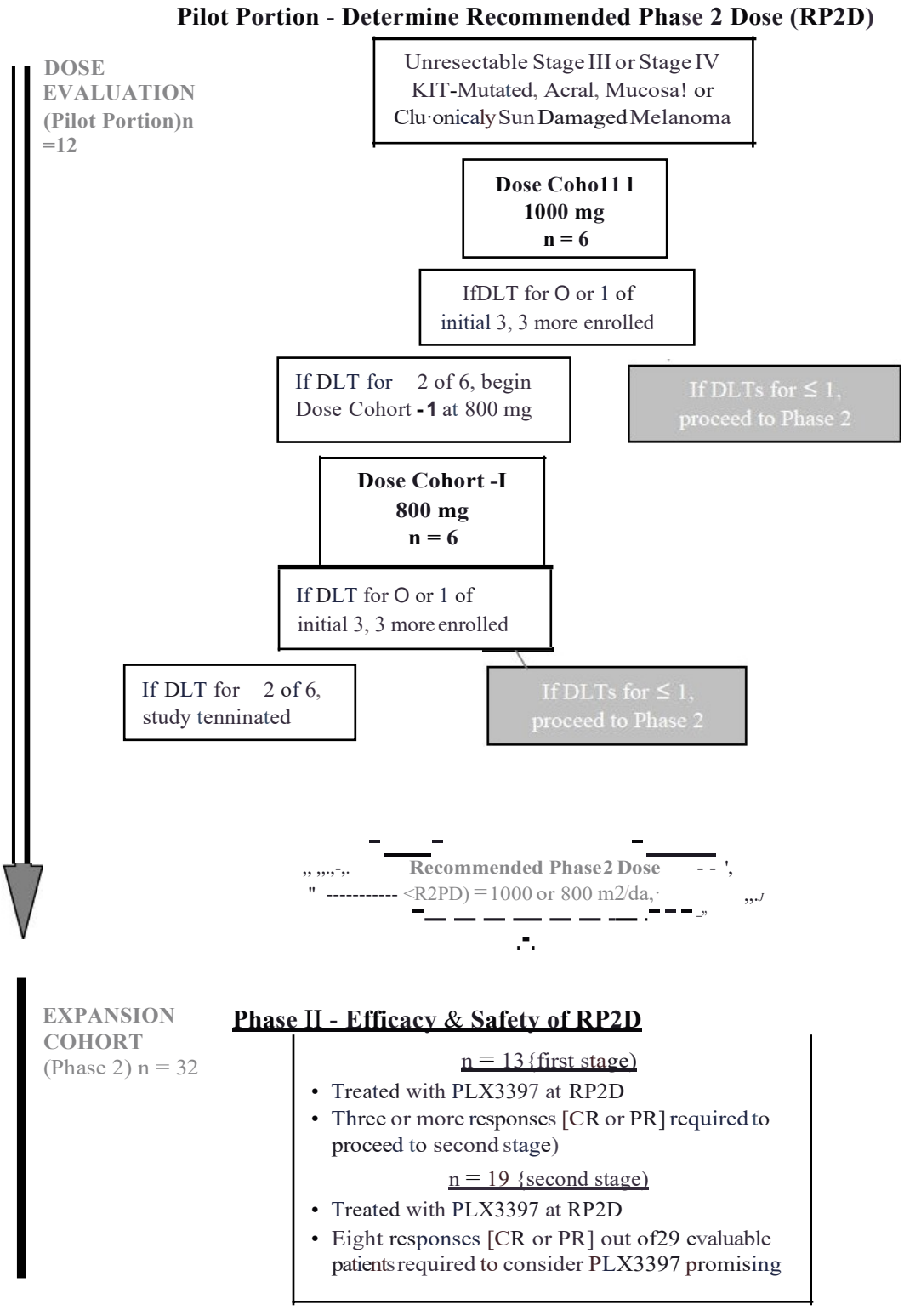

Figure 5-1: Overview of Study PLX3397

5.2. Number of Subjects

Up to approximately 44 patients are planned for enrollment.

Pilot Portion: Approximately 6-12 patients

Phase II: Approximately 32 patients

5.3. Duration of Study

Screening Period:

The Screening period will be 28 days prior to the first dosing for each patient.

Treatment Period:

Subjects will receive study drug twice daily during each 28-day cycle. There is no limit to the number of treatment cycles that can be administered. The treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or a protocol violation.

Those subjects deriving clinical benefit from therapy defined as stable disease or better at the cut-off date, will be offered the opportunity to continue therapy with pexidartinib in the extension phase of this protocol until disease progression, unacceptable toxicity, consent withdrawal, or a protocol violation.

Follow-up Period:

All patients will undergo an End-of-Study evaluation within 28 days of the last dose of study drug and prior to the initiation of any new anti-cancer therapy (if applicable [see Section 8.4]). Thereafter, patients will be contacted by phone every 3 months during year 1 and every 6 months thereafter to obtain information about subsequent treatment(s) and survival status.

6.0 STUDY POPULATION

Patients must meet the inclusion and exclusion criteria to be enrolled in the study, unless a planned protocol deviation is granted by the Sponsor.

6.1. Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study to treatment:

1. Age ≥18 years
2. Unresectable stage III or stage IV melanoma which is histologically confirmed at the treating institution with KIT mutation(s) not known to be resistant to PLX3397.

   Note: Patients with KIT exon 8, 9, 11, 13, and 14 mutations are the most likely to be sensitive to PLX3397. Patients with KIT exon 17 or 18 mutations D816V, Y823D, and A829P should not be enrolled as they are not sensitive to PLX3397. Other KIT exon 17 or 18 mutations may be sensitive to PLX3397 and should be enrolled.
3. No limit on prior systemic therapies for melanoma. Patients who have not received prior therapy are eligible if they have a potentially sensitive KIT mutation.
4. Presence of measurable lesions by RECIST v1.1
5. Eastern cooperative oncology group (ECOG) performance status 0, 1, or 2
6. Life expectancy ≥3 months in the judgment of the investigator
7. Adequate organ and bone marrow function
   a. Absolute neutrophil count (ANC) ≥1.5 X 10^9/L, Hgb ≥10 g/dL, platelet count ≥100 X 10^9/L
   b. AST/ALT ≤2.5 X upper limit of normal (ULN) or <5 X ULN in the presence of liver metastases, total bilirubin ≤1.5 ULN (unless due to Gilbert's Syndrome, in which case it must be ≤2.5 mg/dL), albumin ≥3.0 g/dL
   c. Serum creatinine ≤1.5 X ULN or calculated creatinine clearance (CrCl) >60 mL/min using the Cockcroft-Gault formula

   Patients may be transfused or receive granulocyte-colony stimulating factor (G-CSF) or growth factors.
8. Women of child-bearing potential must have a negative serum pregnancy test at Screening and must agree to use an effective form of contraception from the time of the negative pregnancy test up to 3 months after the last dose of study drug. Effective forms of contraception include abstinence, hormonal contraceptive (injectable or implantable) in conjunction with a barrier method, or a double barrier method. Women of non-child-bearing potential must have been postmenopausal for ≥1 year or surgically sterile.
9. Fertile men must agree to use an effective method of birth control during the study and for up to 3 months after the last dose of study drug.
10. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements

6.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study to treatment:

1. Prior treatment with a KIT inhibitor for melanoma
2. Known presence of NRAS or BRAF mutation
3. Exposure to any chemotherapy, antibody or antibody drug conjugate, small molecule TKI, immunotherapy (e.g., PD-1, PD-L1, or CTLA-4 inhibitors – either antibody or small molecule), investigational drug, or radiation therapy within 28 days prior to Cycle 1 Day 1 (C1D1).
4. Unresolved Grade >1 clinically significant (in the judgment of the investigator) adverse effects from previous therapy prior to C1D1
5. Symptomatic brain metastases. Subjects with untreated brain metastasis ≤1 cm can be considered eligible if deemed asymptomatic by the investigator upon consultation with the medical monitor and do not require immediate radiation or steroids. Subjects with brain metastasis that is treated and stable for 1 month may be considered eligible if they are asymptomatic and on stable dose of steroids or if they do not require steroids following successful local therapy.
6. History of another malignancy (within 2 years prior to first study drug administration) unless malignancy was treated with curative intent and likelihood of relapse is small (<5% in 2 years in the judgment of the investigator). Patients with a history of squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix may be enrolled.
7. Concomitant treatment with other anti-neoplastic agents (hormonal therapy acceptable)
8. Uncontrolled intercurrent or infectious illness
9. Major surgical procedure or significant traumatic injury within 14 days of initiating study drug or anticipation of the need for major surgery during the study
10. Previous radiotherapy to 25% or more of the bone marrow and/or radiation therapy within 28 days prior to C1D1
11. Inability to swallow capsules, or refractory nausea and vomiting, malabsorption, an external biliary shunt, or significant bowel resection that would preclude adequate absorption
12. Congestive heart failure (CHF) New York (NY) Heart Association class III or IV; unstable coronary artery disease (myocardial infarction [MI] more than 6 months prior to study entry is permitted); or serious cardiac arrhythmia
13. Baseline QTcF ≥450 ms (males) or ≥470 ms (females)

14. Known active or chronic infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV). Active or chronic HBV infection is defined as being hepatitis B surface antigen (HBsAg) or HBV DNA-positive. Chronic HCV is defined as being anti-HCV or HCV RNA-positive
15. Known chronic liver disease
16. Women who are breast-feeding or pregnant

7.0 STUDY TREATMENT

7.1. Study Drug Administration

PLX3397 will be supplied in 200 mg capsules and will be taken BID approximately 12 hours apart. Each dose is to be taken with approximately 200 mL of water. Subject will fast for at least one hour before and one hour after dosage. Each cycle of treatment will last 28 days.

The dose level for the Phase II portion of the study will be the RP2D as determined from the Pilot phase. Study drug will be administered BID in a fasting state for at least one hour before and one hour after administration.

Missed doses (generally outside of a 2-hour dosing window) will be skipped and not administered as a double dose at the next administration. Patients who omit their dose will be instructed NOT to make up that dose. Doses that are vomited will not be replaced.

7.2. Dose Levels for Pilot Portion of the Study

7.2.1. Dose Evaluation

During the Pilot portion of the study, 3 to 6 patients in sequential dose cohorts will be enrolled. The dose cohorts are as follows:

- Cohort 1: 1000 mg/day (400 mg in the morning and 600 mg in the evening)
- Cohort -1(if required): 800 mg/day (400 mg BID)

Cohort -1 will be carried out only if Cohort 1 is considered intolerable. Study treatment may be delayed up to 2 weeks to permit resolution of any treatment-related toxicity outside the DLT window.

7.3. Dose Reduction Rules

Dose reduction will occur in accordance with the rules listed below.

- The DLT window is 28 days.

- A minimum of 3 patients will be initially enrolled per cohort.
- If 0 or 1 of the first 3 patients enrolled in a given cohort experiences a DLT, at least 3 additional patients will be enrolled in that cohort.
- If a DLT is observed in one-third or more of patients (e.g., 2 or more of up to 6 patients), the dose combination at which this occurs will be considered intolerable and the maximum tolerated dose (MTD) will have been exceeded and the next lower dose will be evaluated.
- The highest dose level at which 0 or 1 out of 6 experiences a DLT will be declared the MTD. If only 3 patients were initially evaluated at that dose level, an additional 3 patients will be enrolled to evaluate for DLTs at that dose level.
- After dosing has been completed in each cohort, safety and PK data (as applicable) will be reviewed by and dose reduction decisions made by the Sponsor, and investigators and study staff from all participating sites.

7.4. Definitions of Dose-Limiting Toxicity

In the Pilot portion of the study, DLTs will be assessed during a DLT assessment window of 28 days in Cycle 1. However, if clinically relevant ≥Grade 3 cumulative toxicities are observed beyond Cycle 1, these should also be taken into account when assessing further dose reduction.

There will be a 24 hour delay between the first and subsequent patients enrolled in each cohort to maximize the safety of enrolled patients.

Patients who are withdrawn from the study prior to completing the DLT assessment window for any reason other than a DLT will be replaced. Patient numbers must not be re-used.

Subjects who receive less than 80% of the planned dose during the DLT evaluation period will not be considered evaluable and need to be replaced.

A DLT is defined as an AE assessed as being possibly or probably related to study drug administration that is:

- Not due to the underlying malignancy;
- Has no clear evidence of an alternative etiology; and
- Meets one of the following CTCAE v. 4.03 criteria during the first 28 days of PLX3397 administration:
  - Any Grade ≥3 clinically significant hematologic toxicity except:
    - Grade 3 lymphophenia
    - Grade 3 neutropenia ≤7 days
  - Any thrombocytopenia resulting in clinically significant bleeding
  - Any Grade ≥3 clinically significant non-hematologic toxicity except:

- Nausea, vomiting, and/or diarrhea of Grade 3 severity that resolves to Grade ≤2 within 7 days with optimal prophylaxis and/or treatment.
- Grade 3 fatigue that resolves to Grade ≤2 within 7 days.
- Grade ≥3 alkaline phosphatase that is related to underlying malignancy (e.g., bone metastasis)

- If, for any reason, either the Sponsor or principal investigator deems further dose reduction inappropriate. Final decisions on determination of DLTs will be made in consultation between the Sponsor and the principal investigator.
- Any dose reduction required during Cycle 1 due to potential toxicity.
- For the purposes of determining the DLT in Cycle 1, the use of G-CSF or other hematologic growth factors is not permitted during Cycle 1. If a patient develops a protocol defined hematologic DLT and requires the use of G-CSF or other hematologic growth factors, they may be used in accordance with local standard of care, and per Section 7.7.

7.5. Dose-Modification Guidelines

Toxicities that occur outside the DLT window will be taken into consideration when determining the RP2D. Reduction/interruption of dosing for AEs may take place at any time. Below are guidelines for dosage modification for PLX3397–related toxicities as well as guidelines for their management. Dose reductions should occur in increments of 200 mg/day, depending on the toxicity grade, as noted in Table 7-1 and Table 7-2.

These parameters are only a guide and are not intended to supersede the clinical judgment of the treating physician. Medical Monitor should be notified of any dose adjustments. Dosing interruptions longer than 2 weeks for any reason should generally result in discontinuation from the study, unless the patient has demonstrated a clinical benefit from therapy and would like to continue dosing with study drug after discussion between the investigator and the Sponsor. Rechallenge with a reduced dose of pexidartinib may result in a recurrence of increased serum transaminases, bilirubin, or ALP. Monitor liver tests weekly for the first month after rechallenge.

Table 7-1: Dose Modification Guidelines for Treatment-emergent Toxicities

Adverse Reaction	Severity	Pexidartinib Dosage Modifications
Increased ALT and/or AST	Greater than 3 to 5 times ULN	• Withhold and monitor liver tests weekly. • If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose. • If AST or ALT is not less than or equal to 3 times ULN in 4 weeks, permanently discontinue pexidartinib.

	Greater than 5 to 10 times ULN	• Withhold and monitor liver tests twice weekly. If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose. • If AST or ALT is not less than or equal to 3 times ULN in 4 weeks, permanently discontinue pexidartinib.
	Greater than 10 times ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until AST or ALT is less than or equal to 5 times ULN, then weekly until less than or equal to 3 times ULN.
Increased ALP and Gamma-glutamyl transpeptidase (GGT)	ALP greater than 2 times ULN with GGT greater than 2 times ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until ALP is less than or equal to 5 times ULN, then weekly until less than or equal to 2 times ULN.
Increased bilirubin	Total bilirubin greater than ULN to less than 2 times ULN or Direct bilirubin greater than ULN and less than 1.5 times ULN	• Withhold and monitor liver tests twice weekly. • If an alternate cause for increased bilirubin is confirmed and bilirubin is less than ULN within 4 weeks, resume at reduced dose. • If bilirubin is not less than ULN in 4 weeks, permanently discontinue pexidartinib.
	Total bilirubin greater or equal to 2 times ULN or Direct bilirubin greater than 1.5 times ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until bilirubin is less than or equal to ULN.
Adverse reactions or other laboratory abnormalities	Severe or intolerable	• Withhold until improvement or resolution. • Resume at a reduced dose upon improvement or resolution.

Table 7-2: 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.	

For suspected cases of cholestatic liver injury, eg, 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.

7.6. Stopping Rules

Following are the stopping rules for the Pilot portion of the study:

- If ≥2 of 6 patients experience DLTs in cohort 1 (1000 mg/day), Cohort -1 (800 mg per day) will be activated.
- If ≥2 of 6 patients in Cohort -1 experience DLTs, the study will be terminated due to intolerability.

Following are the stopping rules for the Phase II portion of the study:

- Subjects will be discontinued from the study for reasons of AE, clinically significant disease progression, patient request, investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor or institutional review board (IRB)/independent ethics committee (IEC). See Section 7.5 for guidance on dose reduction and discontinuation of therapy for safety concerns. Noncompliant patients may be replaced.

Patients will be discontinued from the study if they are off study drug for more than 2 weeks, regardless of the reason, unless the patient has demonstrated a clinical benefit from therapy and

would like to continue dosing with study drug after discussion between the investigator and the Sponsor.

The Pilot and Phase II portions of the study may be discontinued if the study is terminated by the Sponsor, the China Food and Drug Administration (CFDA), or other regulatory authorities.

7.7. Concomitant Medications (and Procedures)

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 electronic case report form (eCRF), including the reason for treatment, generic name of the drug, dosage, route, and start and stop dates of administration.

For the purposes of determining the DLT in Cycle 1, the use of G-CSF or other hematologic growth factors is not permitted during Cycle 1. If a patient develops a protocol defined hematologic DLT and requires the use of G-CSF or other hematologic growth factors, they may be used in accordance with local standard of care.

Patients enrolled in studies with PLX3397 who are also receiving concomitant warfarin should have their anti-coagulation status carefully monitored, especially shortly after initiation of PLX3397, for the potential need to make adjustments in warfarin dosing. In particular, INR should be obtained just prior to initiation of PLX3397, within 1 to 2 weeks after initiation, and periodically thereafter. Dose adjustments of warfarin should be made as medically indicated.

Patients are discouraged from taking proton pump inhibitors or other strong anti-acids (e.g., H-2 antagonists) as these may interfere with the reliable identification of the R2PD.

7.7.1. CYP3A inducers

Avoid the concomitant use of strong CYP3A inducers, including St John's wort (see ATTACHMENT 2, a list of common CYP3A inhibitors and inducers).

7.7.2. CYP3A and UGT inhibitors

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

Of the five major CYP isoforms, 3A4 (BFC) may be involved in Phase 1 metabolism of PLX3397, with possibly CYP1A2 playing a minor role (see ATTACHMENT 2 for a list of common CYP3A inhibitors and inducers). In general, strong inducers of CYP3A4 should be avoided unless absolutely clinically necessary. These include anticonvulsants, mycin,

antimicrobials, and antiretrovirals. Some common examples include inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.

Avoid concomitant use of pexidartinib with moderate or strong CYP3A inhibitors or UGT inhibitors. If concomitant use with a moderate or strong CYP3A inhibitor or UGT inhibitor cannot be avoided, reduce the pexidartinib dose according to the recommendations in Table 7.3. If concomitant use of a moderate or strong CYP3A inhibitor or UGT inhibitor is discontinued, increase the pexidartinib dose (after 3 plasma half-lives of the moderate or strong CYP3A inhibitor or UGT inhibitor) to the dose that was used before starting the inhibitor.

Table 7-3: Recommended Dosage Reductions for Pexidartinib with Concomitant Use of Moderate or Strong CYP3A Inhibitors or UGT Inhibitors

Current Total Daily Dose	Modified Total Daily Dose	Administration of Modified Total Daily Dose
800 mg	400 mg	200 mg twice daily
600 mg	400 mg	200 mg twice daily
400 mg	200 mg	200 mg once daily

7.7.3. Hormonal Contraceptives

Pexidartinib has been indicated to be a moderate CYP3A4 inducer, as concurrent administration of pexidartinib decreased the AUCinf of the CYP3A4 substrate midazolam by 57%. As the hormonal contraceptive ethinyl estradiol is a CYP3A4 substrate, there is a potential that exposure of ethinyl estradiol may decrease on concurrent administration with pexidartinib. As pexidartinib may cause embryo-fetal harm when administered to a pregnant woman, females of reproductive potential should be advised to use an effective, non-hormonal method of contraception during treatment with pexidartinib and for 1 month after the last dose. Males with female partners of reproductive potential should be advised to use an effective method of contraception during treatment with pexidartinib and for 1 month after the last dose. Female partners of male patients should concurrently use effective contraceptive methods (hormonal or non-hormonal).

7.7.4. Acid-reducing Agents

Avoid the concomitant use of proton pump inhibitors (PPIs) while taking pexidartinib. As an alternative to a PPI, administer pexidartinib 2 hours before or 2 hours after taking a locally-acting antacid, or if using a histamine 2 (H2)-receptor antagonist, administer pexidartinib at least 2 hours before or 10 hours after taking an H2-receptor antagonist.

7.8. Dosage Modification for Renal Impairment

The recommended dosage of pexidartinib for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min estimated by Cockcroft-Gault using actual body weight) is 200 mg in the morning and 400 mg in the evening.

7.9. Precautions and Restrictions

Because pexidartinib is a substrate for CYP3A4/5 and some fruits are CYP3A4/5 inhibitors, foods or beverages containing CYP3A4/5 inhibiting fruits (eg, grapefruit, pomelo, star fruit, and pomegranate) should be avoided throughout the study.

7.10. Management of Clinical Events

All necessary support care will be available to patients. For dose-modification guidelines, see Section 7.5.

7.11. Blinding and Unblinding

Blinding methods will not be employed; PLX3397 will be administered in open-label fashion.

7.12. Preparation, Reconstitution, and Dispensation

PLX3397 is an anticancer drug, and as with other potential toxic compounds, caution should be exercised when handling PLX3397 (see Section 7.14). Specific instructions on preparation, reconstitution, and dispensation will be provided in the PLX108-13 Pharmacy Manual.

7.13. Packaging and Labeling

PLX3397 capsules (200 mg strength) are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) and GCP at the following address:

Catalent Pharma Solutions
10245 Hickman Mills Drive
Kansas City, MO 64137, USA

7.14. Storage, Handling, and Accountability

PLX3397 capsules will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature, between 15º–30ºC (59º–86ºF). Patients will be requested to store the study drug at the recommended storage conditions noted on the label, out of the reach of children or other cohabitants.

The Study drug provided in accordance with this Protocol will be kept in a secure place, and will only be supplied to Subjects participating in this Study. The Principal Investigator is accountable for all Study drug supplied by the Sponsor in accordance with this Protocol. In addition, the Principal Investigator must keep accurate and up-to-date dispensation records. Any Study drug accidently or deliberately destroyed must be recorded in a timely fashion, including an explanation for the destruction in writing. Any discrepancies between the amounts of Study drug dispensed and returned must also be explained in writing. All such records of drug accountability must be entered on the corresponding Subject CRF's.

All unused and partially used Study drug must be returned to the designee as instrusted by the Sponsor, or destroyed on Site in accordance with the established procedures for drug destruction, and with approval by the Principal Investigator or his/her designee. Details of destruction, including, but not limited to, the number of boxes destroyed, batch number, and the date and method of destruction must be recorded on the Study drug destruction logs.

7.15. Other Protocol-Specified Materials

There are no other supplies or materials required by the Protocol.

8.0 STUDY CONDUCT

8.1. Study Personnel and Organizations

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 (Sponsor)	[redacted] Daiichi Sankyo, Inc. 211 Mount Airy Road Basking Ridge, NJ 07920, US [redacted]

SAE and Potential Hy's Law case Reporting Contact:	The investigator will ensme that the SAE repo1ting fo1m is completed and E-mailed/eFaxed to the following address within 24 homs of learning of the occmTence: • SAE • Hepatic events meeting combination abno1malities [ALT or AST 3 X ULN with simultaneous total bilirnbin 2 X ULN] (potential Hy's Law case), both serious and nonserious (see Section 13.0 for details) Name: DSI CSPV Safety Phone: [redacted] Fax: [redacted] Email: CSPV-Clinical@dsi.com/ [redacted]

8.2. Arrangements for Recruitment of Subjects

Recrnitment and enrollment strategies for this study may include recrnitment from the investigator's local practice or refe1rnls from other physicians. If adveitisements become pa1t of the recrnitment strategy, they will be reviewed by IRB and/or IEC. Subjects will be compensated for their paiticipation in this study.

8.3. Treatment Group Assignments

This is an open-label, sequential dose-escalation study with an expansion coho1t. The initial dose level of PLX3397 will be 1000 mg/day administered BID. Thereafter, dose de-escalation will occm as described in Section 7.2.1. The expansion cohort will be enrolled at the RP2D according to inclusion and exclusion criteria (Section 6.1 and Section 6.2).

8.4. Withdrawal of Patients from Drug Treatment, Study and Patient Replacement

The Medical Monitor will monitor safety data throughout the course of the study. The Medical Monitor will review SAEs within timeframes mandated by company procedmes and will review trends, laborato1y data, and AEs at periodic inte1vals and provide for interim safety analyses if appropriate.

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, AE, clinically significant disease progression, patient request, investigator decision,

protocol violation, patient noncompliance, and study termination by the Sponsor or IRB/IEC. When a patient discontinues or is withdrawn, the investigator will notify the Sponsor and should perform the procedures indicated in the End of Study column in the Schedule of Events within 28 days after discontinuation of study drug and before initiation of any new anti-cancer therapy. Follow-up information will be obtained for patients who discontinue their participation in or are withdrawn from the study.

Patients withdrawn from the study for reasons other than toxicity or clinically significant disease progression (e.g., protocol violation or noncompliance) may be replaced at the discretion of the medical monitor and the investigator. Study drug administration may be discontinued due to an AE or at the discretion of the investigator.

The consequence of withdrawal of consent by a patient will be that no new information will be collected from that patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety.

8.5. Study Compliance

The study drug PLX3397 will be provided only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Any discrepancy regarding the dose administered and the reason for the discrepancy will be recorded in the eCRF. At each clinic visit, patients will be questioned about their compliance with study drug administration, and their dosing diary should be reviewed.

9.0 STUDY ASSESSMENT SCHEDULE

Event schedules are summarized in Table 2-1 and Table 2-2.

All patients must provide written informed consent. During the consent process, the person obtaining consent must inform the patient of all elements of the study. No protocol-specific procedures, including screening procedures, are to be performed until the patient has signed and dated an IRB/IEC-approved informed consent form. The study begins with the signing and dating of the informed consent form.

A patient will be considered enrolled in the study once all inclusion and exclusion criteria have been met, and the completed patient enrollment form has been submitted to the CRO, signed by the appropriate representative, and returned to the investigative site.

Screening procedures are to be performed within 28 days before C1D1 of study therapy.

The end of the study is defined as the date of the last dose of PLX3397 (see Section 8.4 for reasons for discontinuation or withdrawal of a patient from the study).

9.1. Pilot Portion—All Cohorts

The schedule of events for patients in all cohorts in the Pilot portion is summarized in Table 2-1 and detailed in the subsections below.

9.1.1. Screening Visit (Day –28 to Day –1)

- Informed consent
- Medical history
- Height and weight
- Complete physical examination
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- 12-lead ECG
- ECOG performance status evaluation
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), and prothrombin time/international normalized ratio (PT/INR)
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- Documentation of archival tissue availability
- KIT mutation documentation
- Computed Tomography (CT) chest, abdomen, and pelvis (PET/CT scan may be used as well)
- Adverse event assessment

9.1.2. Screening Visit (Day –7 to Day –1)

- Pregnancy test (for women of childbearing potential). For women of child-bearing potential, a serum pregnancy test at Screening must be negative.
- Concomitant medications

9.1.3. Cycle 1, Day 1

Procedures to be performed before the morning dose:

- Fresh tumor biopsy (may be performed within 3 days prior to the study visit)
- Blood sampling for PK analysis
- Blood sampling for PD analysis
- Physical examination (symptom-directed)
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- ECOG performance status
- PET scan (–3-day window) (If a PET/CT scan is performed, then no additional PET scan is needed.)
- Adverse event assessment
- Concomitant medications

Procedures to be performed *after* the morning dose:

- Blood sampling for PK analysis (0.5, 1, 2, 4, and 6 hours post-dose [± 10 minutes at the 0.5- and 1-hour post-dose timepoints, and ± 30 minutes at the 2-, 4-, and 6-hour post-dose timepoints])

9.1.4. Cycle 1, Day 8 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Adverse event assessment
- Concomitant medications

9.1.5. Cycle 1, Day 15 ± 3 days

Procedures to be performed *before* the morning dose:

- Fresh tumor biopsy (optional, and may be performed within 3 days prior to the study visit)
- Blood sampling for PK analysis
- Blood sampling for PD analysis
- 12-lead ECG
- Physical examination (symptom-directed)
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- ECOG performance status assessment
- Adverse event assessment
- Concomitant medications
- Study drug compliance via study drug diary review and accountability

Procedures to be performed *after* the morning dose:

- Blood sampling for PK analysis (0.5, 1, 2, 4, and 6 hours post-dose [± 10 minutes at the 0.5- and 1-hour post-dose timepoints, and ± 30 minutes at the 2-, 4-, and 6-hour post-dose timepoints])
- 12-lead ECG (2 hours (± 30 minutes) post-dose)

9.1.6. Cycle 1, Day 22 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Adverse event assessment

- Concomitant medications

9.1.7. Cycle 2, Day 1 ± 3 days

Procedures to be performed *before t*he morning dose:

- Physical examination (symptom-directed)
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- 12-lead ECG
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- ECOG performance status
- Adverse event assessment
- PET scan (±3-day window) (If a PET/CT scan is performed, then no additional PET scan is needed.)
- Concomitant medications
- Study drug compliance via study drug diary review and accountability

Procedures to be performed *after* the morning dose:

- 12-lead ECG (2 hours (± 30 minutes) post-dose)

9.1.8. Cycle 2, Day 8 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count

9.1.9. Cycle 2, Day 15 ± 3 days

- Physical examination (symptom-directed)
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- ECOG performance status
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Adverse event assessment
- Concomitant medications
- Study drug compliance via study drug diary review and accountability

9.1.10. Cycle 2, Day 22 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count

9.1.11. Cycle 3+, Day 1 ± 3 days

Patients will continue treatment beyond Cycle 2 if they tolerate the drug well and experience no disease progression.

Procedures to be performed *before* the morning dose:

- Physical examination (symptom-directed)
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH;
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature;

- ECOG performance status assessment
- Adverse event assessment
- Concomitant medications
- Study drug compliance via study drug diary review and accountability
- CT chest, abdomen, and pelvis (performed every 8 weeks during the first 24 weeks of study treatment, then every 12 weeks thereafter [e.g., at the end of Cycles 4, 6, then 9, 12, 15, and onward]) (PET/CT scan may be used as well)

9.1.12. Extension phase

Subjects receiving clinical benefit (SD, PR, or CR) from study treatment at the time of data cut-off of the main study, will be offered the opportunity to continue pexidartinib treatment in an extension phase.
Procedures to be performed before the morning dose in the extension phase include:

- Physical examination (symptom-directed)
- Serum chemistry: sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH;
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Vital signs: blood pressure, respiratory rate, pulse rate, and body temperature;
- Adverse event assessment
- Study drug compliance via study drug diary review and accountability
- CT chest, abdomen, and pelvis (performed every 12 weeks) (PET/CT scan may be used as well)

Subjects will continue in the extension phase until disease progression, unacceptable toxicity or withdrawal of consent.

9.1.13. End-of-Study visit

The End-of-Study visit is scheduled within the 28-day period after the last dose of study drug and before starting any new anti-neoplastic therapy.

Procedures to be performed:

- Fresh tumor biopsy (optional)
- Weight

- Physical examination (complete)
- 12-lead ECG
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH;
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature;
- ECOG performance status assessment
- Adverse event assessment
- Concomitant medications

9.1.14. Post-Study Follow-up

Telephone contact by study staff will be conducted every 3 months during Year 1, then every 6 months thereafter to obtain information on survival status and any new anti-cancer therapies received.

9.2. Phase II - Expansion Cohort

The schedule of events for patients in the Phase II portion of the study is summarized in Table 2-2 and detailed in the subsections below.

9.2.1. Screening Visit (Day –28 to Day –1)

- Informed consent
- Medical history
- Height and weight
- Complete physical examination
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- 12-lead ECG
- ECOG performance status evaluation
- Serum chemistry: including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, LDH, and PT/INR

- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- Documentation of archival tissue availability
- KIT mutation documentation
- CT chest, abdomen pelvis (PET/CT scan may be used as well)
- Adverse event assessment

9.2.2. Screening Visit (Day –7 to Day –1)

- Pregnancy test (for women of childbearing potential). For women of child-bearing potential, a serum pregnancy test at Screening must be negative.
- Concomitant medications

9.2.3. Cycle 1, Day 1

Procedures to be performed *before* the morning dose:

- Blood sampling for PD analysis
- Whole blood for circulating tumor DNA (ctDNA) (Korea sites only)
- Fresh tumor biopsy (first 13 patients enrolled in Phase II; –3-day window)
- Physical examination (symptom-directed)
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- ECOG performance status
- Adverse event assessment
- PET scan (–3-day window) (If a PET/CT scan is performed, then no additional PET scan is needed)

- Concomitant medications

9.2.4. Cycle 1, Day 8 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Adverse event assessment
- Concomitant medications

9.2.5. Cycle 1, Day 15 ± 3 days

Procedures to be performed *before* the morning dose:

- Blood sampling for PD analysis
- Fresh tumor biopsy (optional, first 13 patients enrolled in Phase II; –3-day window)
- 12-lead ECG
- Physical examination (symptom-directed)
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- ECOG performance status assessment
- Adverse event assessment
- Concomitant medications
- Study drug compliance via study drug diary review and accountability

Procedures to be performed *after* the morning dose:

- 12-lead ECG (2 hours (± 30 minutes) post-dose)

9.2.6. Cycle 1, Day 22 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH;
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Adverse event assessment
- Concomitant medications

9.2.7. Cycle 2, Day 1 ± 3 days

Procedures to be performed *before* the morning dose:

- Physical examination (symptom-directed)
- 12-lead ECG
- Whole blood for ctDNA (Korea sites only)
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- ECOG performance status
- Adverse event assessment
- PET scan (±3-day window) (If a PET/CT scan is performed, then no additional PET scan is needed)
- Concomitant medications
- Study drug compliance via study drug diary review and accountability

Procedures to be performed *after* the morning dose:

- 12-lead ECG (2 hours (± 30 minutes) post-dose)

9.2.8. Cycle 2, Day 8 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count

9.2.9. Cycle 2, Day 15 ± 3 days

- Physical examination (symptom-directed)
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature
- ECOG performance status
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Adverse event assessment
- Concomitant medications
- Study drug compliance via study drug diary review and accountability

9.2.10. Cycle 2, Day 22 ± 3 days

- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count

9.2.11. Cycle 3+, Day 1 ± 3 days

Patients will continue treatment beyond Cycle 2 if they tolerate the drug well and experience no disease progression.

Procedures to be performed *before* the morning dose:

- Physical examination (symptom-directed)

- Whole blood for ctDNA (Korea sites only)
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH;
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Urinalysis, including pH, protein/albumin, glucose, nitrites, ketones/acetone, and hemoglobin/blood
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature;
- ECOG performance status assessment
- Adverse event assessment
- Concomitant medications
- Study drug compliance via study drug diary review and accountability
- CT chest, abdomen pelvis (performed every 8 weeks during the first 24 weeks of study treatment, then every 12 weeks thereafter [e.g., at the end of Cycles 4, 6, then 9, 12, 15, and onward]) (PET/CT scan may be used as well)

9.2.12. End-of-Study visit

The End-of-Study visit is scheduled within the 28-day period after the last dose of study drug and before starting any new anti-neoplastic therapy.

Procedures to be performed:

- Fresh tumor biopsy (optional, first 13 patients enrolled in Phase II; –3-day window)
- Weight
- Physical examination (complete)
- 12-lead ECG
- Whole blood for ctDNA Korea sites only.
- Serum chemistry, including sodium, potassium, chloride, CO_2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilirubin, AST, ALT, alkaline phosphatase, GGT, and LDH;
- Hematology: hemoglobin, hematocrit, white blood cell count with a differential, platelet count
- Vital signs, including blood pressure, respiratory rate, pulse rate, and body temperature;
- ECOG performance status assessment

- Adverse event assessment
- Concomitant medications

9.2.13. Post-Study Follow-up

Telephone contact by study staff will be conducted every 3 months during Year 1, then every 6 months thereafter to obtain information on survival status and any new anti-cancer therapies received.

9.3. Study Procedures

9.3.1. Electrocardiograms

Patients should rest in the supine 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, respiratory rate (RR), PR interval, QRS interval, QT interval, and QTcF interval.

9.3.2. KIT Mutation Documentation

KIT mutation(s) must be documented prior to enrollment. Patients with KIT exon 8, 9, 11, 13, and 14 mutations are the most likely to be sensitive to PLX3397. Patients with KIT exon 17 or 18 mutations D816V, Y823D, and A829P should not be enrolled as they are not sensitive to PLX3397. Other KIT exon 17 or 18 mutations may be sensitive to PLX3397 and should be enrolled.

Table 9-1: Summary of Known KIT Mutations in Melanoma and Their Sensitivity to PLX3397 and Other Approved Drugs

Exon	Mutation	Be08[a]	Be08-cited[b]	Total	Imatinib	PLX3397	Sunitinib	Dasatinib	Sorafenib
11	Y553N		1	1		S			
11	W557R	1	1	2		S			
11	K558N	1		1		S			
11	V559A	1	2	3		S			
11	V559D	1		1	0.063 (Gu07)	S		0.027 (Gu07)	0.066 (Gu07)
11	V560A	1		1		S			
11	V560D	1		1	0.1 (He08)	S (V560G <0.016)			
11	V569G		1	1		S			
11	L576P	5	7	12	poor	S			
13	K642E		9	9		S			
17	D816H		2	2	2.6	0.1	0.1	0.002	
17	Y823D	1		1	R	R	R (He08)		
18	A829P	1	1	2	~0.2 (He08)	R	R (He08)		
Total		13	24	37					

Note: IC_{50} (μM) is listed if available (either from literature or sponsor's own assay data); otherwise sensitivity is indicated qualitatively by S (sensitive) or R (resistant). In the latter case, the sensitivity for each mutation was deduced based on 1) structure-based prediction of the effect of the mutation on the binding of PLX3397 to KIT and/or 2) the activity of other inhibitors (e.g., dasatinib) with analogous binding mode(s).

[a] Beadling 2008.

[b] Other studies cited in Beadling 2008.

9.3.3. Fresh Tissue Biopsy Samples (Pilot Portion and First 13 Patients of Phase II Portion of the Study)

A pre-dose tumor biopsy of a progressive lesion will be obtained in patients with accessible tissue. Formalin-Fixed Paraffin-Embedded (FFPE) tissue slides will be collected and stored for subsequent evaluation using project-specific tumor assays to be performed at one or more central laboratories.

9.3.4. PET Scans (Pilot Portion and First 13 Patients of Phase II Portion of the Study)

^{18}FDG-PET scans will be obtained at Day 1 of Cycle 1 and at Day 1 of Cycle 2. Patients should be instructed to fast for at least 6 hours (if feasible) prior to ^{18}FDG administration to maintain basal levels of plasma glucose and insulin. They are encouraged to keep drinking water to maintain hydration and limit radiation to the urinary tract. Plasma glucose levels will be determined before administration of ^{18}FDG to document euglycemia.

The dose of ^{18}FDG will be administered intravenously according to weight (0.15 mCi/kg, ranging from 3 to 16 mCi) and images will be acquired after approximately 60 minutes distribution time. Images will be obtained over the entire body from the base of the skull to mid-thigh, including brain and extremities when clinically relevant.

^{18}FDG PET emission images will be corrected for attenuation. ^{18}FDG PET scanning should be performed prior to biopsy collection procedure to avoid false positive results.

10.0 STUDY ENDPOINTS

10.1. Pilot Portion

The endpoints in the Pilot portion of the study include:

- DLTs will define the RP2D (1000 mg per day or 800 mg per day)
- Safety endpoints (i.e., AEs, clinical laboratory evaluations, ECGs, physical examinations, and vital sign measurements)
- Pharmacokinetic (PK) analysis
- Serum/plasma tumor biomarkers including CSF-1

The exploratory endpoints in the Pilot portion of the study include:

- Immunohistochemistry (IHC) and molecular analysis of archival and paired fresh tumor biopsy
- PET scan evaluation on Day 1 of Cycle 2 compared to Baseline

10.2. Phase II

The primary endpoint in the Phase II portion of the study includes:

- Objective response rate (ORR), which is the sum of CR and PR by RECIST v1.1

The secondary endpoints in the Phase II portion of the study include:

- Duration of response (DoR)
- Progression free survival (PFS)
- Overall survival (OS)
- Safety endpoints (i.e., AEs, clinical laboratory evaluations, ECGs, physical examinations, and vital sign measurements)

The exploratory endpoints in the Phase II portion of the study include:

- IHC and molecular analysis of archival and paired fresh tumor biopsy
- Serum/plasma tumor biomarkers including CSF-1
- Positron emission tomography (PET) scan evaluation on Day 1 of Cycle 2 compared to Baseline

11.0 STATISTICAL AND QUANTITATIVE ANALYSES

11.1. Determination of Sample Size

The Pilot portion of this study will determine if 1000 mg PLX3397 is an appropriate dose for the Phase II portion of the study. Traditional 3+3 design will be utilized to determine RP2D.

Eligible patients will enter the study in sets of three. Dose-limiting toxicity (DLT) is defined in Section 7.4. If 0 or 1 of 3 patients at the 1000 mg dose level cohort experience DLT, 3 additional patients will be enrolled for a total of 6 patients. If ≥2 of 6 patients experience DLT at the 1000 mg dose, the dose will be de-escalated to 800 mg per day. If 0 or 1 of 3 patients at the 800 mg dose level cohort experiences DLT, 3 additional patients will be enrolled for a total of 6 patients. If ≥2 of 6 patients experience DLT at the 800 mg dose, the study will be terminated due to intolerability. Each cohort of patients will be observed for toxicity for 28 days in order to allow time to identify all acute effects of PLX3397. Between 6 and 12 patients will be accrued for the Pilot portion of this study.

The primary objective of the Phase II portion of this study is to evaluate the objective response rate (ORR) at the RP2D. The RP2D will be either the MTD or the alternate dose level below the MTD determined by sponsor and investigator. A true response rate of 40% or more will be considered promising while 15% or lower will not be considered as evidence of activity.

A Simon two-stage design with 90% targeted power and one-sided type I error of 5% will be employed for this study. With the assumption of 10% drop-out, the total sample size will be 32 patients to achieve 29 evaluable patients. During stage one, 13 evaluable patients will be enrolled. If there are 3 or more responses (CR+PR) observed, then the study will continue to the second stage of accrual, and 16 evaluable patients will be enrolled in the second stage. If there are 8 or more responses observed among 29 evaluable patients, the treatment will be considered promising.

With this design, the probability of terminating the study after 13 patients is 69% if the true response rate is 15%. The probability that the treatment will be considered promising is 5%, if the true response rate is 15%, and 90.7% if the true response rate is 40%. Allowing for a 10% unevaluability rate, the overall accrual goal will be 32 patients for the Phase II portion of this study.

11.2. Randomization and Stratification

No randomization or stratification of patients is planned for this study.

11.3. Populations for Analysis

The primary population for safety will consist of patients who signed the informed consent and have any follow-up data after receiving at least one dose of study drug. The primary population for efficacy will consist of the modified ITT population, i.e., patients who a) fulfill inclusion/exclusion criteria, b) have a baseline CT scan at screening, and c) have at least one on-study CT scan to assess tumor response to study drug, or early progression of disease or death prior to first tumor assessment during treatment period.

The main study will be closed at the cut-off date and the data will be followed in ongoing subjects in the extension part. Data collected in the extension part will be reported separately from the clinical study report.

11.4. Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in the data listings and tabulations. No imputation of values for missing data will be performed.

11.5. General Methodology

Summary of tabulations will be presented by treatment group displaying the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data.

11.6. Baseline Comparisons

Demographic and baseline characteristics will be summarized by treatment group.

11.7. Efficacy Analysis

The Phase II portion of the study will follow a Simon two-stage design to compare a null ORR of 15% with an alternative ORR of 40% with 90% power and a one-sided type I error of 5%. The total sample size will be 29 evaluable patients. Thirteen patients will be enrolled in the first stage, with at least three responses required to proceed to the second stage. Eight responses among 29 patients are required for PLX3397 to be considered promising. See Section 11.10 for discussion of interim analysis.

Object tumor response to treatment will be evaluated using investigator-determined RECIST v1.1 (ATTACHMENT 3). PFS, OS and duration of response will be evaluated as secondary efficacy endpoints. PFS will be calculated for each patient as the number of days from study

enrollment to the date of the first documented disease progression or date of death from any cause, whichever occurs first. Overall survival is defined as the time from study enrollment to death from any cause, censoring at the date of last contact or the end of the study. Duration of response (DoR) is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of disease progression or to death due to any cause, whichever occurs first. DoR will only be calculated for the subgroup of patients with a confirmed objective tumor response. Sponsor may request imaging data for the confirmation of the tumor response.

The Kaplan-Meier method will be used to estimate the median PFS, OS and DoR.

11.8. Pharmacokinetics/Pharmacodynamics/Biomarkers

11.8.1. Pharmacokinetic Analysis

The PK profile of plasma PLX3397 will be analyzed by measurement of area under the plasma concentration-time curve (AUC_{0-6}), peak concentration (C_{max}), and time of maximum observed concentration (T_{max}). To evaluate plasma exposure accumulation after repeated dosing, accumulation ratios of Day 15 to Day 1 for AUC_{0-6} and C_{max} (R_{obs} and RC_{max}, respectively) will be determined.

11.8.2. Pharmacodynamic Analysis

No formal statistical analysis of PD endpoints will be performed. PD data from each assay will be listed, and possible relationships between clinical response and PD variables will be explored. Any biological activity will be described.

11.8.3. Tissue Evaluation

At least 10 unstained FFPE slides of 5 µm thickness from the archival tissue should be submitted on all participants in the study. The archival tissue may be from the original diagnosis, or from a biopsy obtained after a previous therapy. Slides should be air-dried (NOT baked) onto positively charged slides. A representative paraffin block can also be provided, which will be returned to the study site after sectioning. For patients undergoing paired fresh biopsy, at least 10 sections are also requested, and at least 20 unstained FFPE slides of 5 µm thickness from the fresh tissue should be submitted (Phase I and first 13 patients enrolled in Phase II).

Exploratory tissue studies will include IHC for KIT, pERK, Ki67. Tissue may also be used for KIT or other oncogene mutation sequencing confirmation. Other exploratory evaluations may include assessment of the tumor microenvironment by IHC or other methods for immune cell expression/number (e.g., PD-1). Exploratory blood studies will measure CSF-1 and ctDNA (Phase II portion in Korea only). Planned biomarkers are listed in ATTACHMENT 1.

11.9. Safety Analysis

Safety variables to be assessed will include AEs, laboratory test results (hematology, serum chemistry, and urinalysis), ECG, weight, and vital signs.

Adverse event terms recorded on the eCRFs will be mapped to preferred terms using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 17.0 or later. All AEs will be summarized according to the system organ class and preferred term within the organ class. Adverse events will be tallied for overall frequency (number and percentage of patients), worst reported severity, and relationship to study drug for each preferred term per patient. SAEs will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

Laboratory variables will be examined using mean change in value from baseline to scheduled time points. Laboratory values will also be categorized according to their CTCAE (version 4.03) toxicity grade and tabulated by worst on-study toxicity grade. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first PLX3397 dose.

ECG, weight, and vital signs will also be summarized by changes from baseline to scheduled time points using descriptive statistics. Changes in QTcF will also be evaluated for the proportion of patients with absolute values >500 msec and change from baseline >60 msec.

11.10. Interim Analysis

The Phase II portion of the study will follow a Simon two-stage design to compare a null ORR of 15% with an alternative ORR of 40% with 90% power and a one-sided type I error of 5%. The total sample size will be 29 evaluable patients. Thirteen patients will be enrolled in the first stage before triggering an interim analysis. At least three responses are required to proceed to the second stage. Eight responses among 29 patients are required for PLX3397 to be considered promising.

12.0 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowable by local regulations.

13.0 EVENTS OF SPECIAL INTEREST

13.1. Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or nonserious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case (ALT or AST ⩾3×ULN with simultaneous total bilirubin ⩾2×ULN) should always be reported to the Sponsor using a SAE reporting form along with the investigator's assessment of seriousness, causality, and a detailed narrative. These events should be reported within 24 h of the investigator's awareness of the events.

If the subject discontinues the study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations in order to determine the cause and severity of the potential liver injury.

14.0 ADVERSE EVENTS

14.1. Definitions

14.1.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug. Clear progression of the underlying cancer and hospitalizations due to the progression of cancer should not be reported as an AE, or a SAE. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional.
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a study drug.
- An AE that has been associated with the discontinuation of the use of a study drug.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)

- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Adverse events will be graded in severity according to CTCAE v4.03 criteria.

14.1.2. Serious Adverse Event Definition

A SAE is any AE, occurring at any dose and regardless of causality that:

- Results in **death**
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect
- Is an important medical event. An 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 one 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.

Clarification should be made between the terms "serious" and "severe" because they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.1.3. Disease Progression

Clear progression of the underlying cancer and hospitalizations due to the progression of cancer should not be reported as an AE, or a SAE. Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of underlying cancer, the finding should be reported as an AE or SAE as appropriate.

14.2. Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs that occur during the course of the study, as defined in Section 14.3, must be reported by the investigator to the sponsor or designee by faxing or e-mail the SAE Form immediately after the investigator becomes aware of the SAE. In addition, all SAEs including all deaths that occur up to and including 21 ± 7 days after administration of the last dose of study drug or prior to the administration of any new anti-cancer therapy, whichever occurs first, must be reported to DSI CSPV Safety within 24 hours of site awareness of the event. ALL SAEs and deaths must be reported whether or not considered causally related to the study drug. The SAE Form, created specifically by the sponsor, will be provided to each clinical study site. The information collected will include a minimum of the following: patient number; a narrative description of the event; and an assessment by the investigator as to the intensity of the event and relatedness to study drug. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE may be requested by the sponsor. SAEs reported to DSI CSPV Safety must match the data provided on the CRF.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

For both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Oncology Studies: Intensity for each AE, including any lab abnormality, will be determined by using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, as a guideline, wherever possible. The criteria are provided in the Study Manual and also are available online at http://ctep.cancer.gov/reporting/ctc.html. In those cases where the NCI CTC criteria do not apply, intensity should be defined according to the following criteria:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities

Relatedness to study drug administration will be determined by the investigator responding to the question, 'Is there a reasonable possibility that the AE is associated with the study drug?' Relatedness to study drug administration will be graded as "probably," "possibly," or "not related," as follows:

Not Related	Another cause of the event is most plausible; *or,* Clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration; *or,* A causal relationship is considered biologically implausible.
Possibly Related	An event that follows a reasonable temporal sequence from administration of the study treatment or a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.
Probably Related	An event that follows a reasonable temporal sequence from administration of the study treatment, *and*, There is a biologically plausible mechanism for study treatment causing or contributing to the AE, *and*, The event could not be reasonably explained by the known characteristics of the patient's clinical state. In addition, the relationship may be confirmed by improvement on stopping the study treatment and reappearance of the event on repeated exposure.

14.3. Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths will be recorded on the CRFs up to and including the last visit within 28 days after administration of the last dose of study drug and prior to the administration of any new anti-cancer therapy. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or inter-current illness(es). The AE collection period will begin when the patient signs informed consent.

Any SAE that occurs at any time after completion of the study and the designated follow-up period, which the investigator considers to be related to study drug, must be reported to the sponsor.

14.4. Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

Daiichi Sankyo must be notified of any female patient or any male patient whose female partner becomes pregnant while receiving or within 3 months of discontinuing the study drug. Reporting after follow-up visit or early termination is done voluntarily by the Investigator.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator or designee to report any pregnancy in a female patient or a male patient's female partner to DSI CSPV Safety using the Exposure In Utero (EIU) Reporting Form. The Investigator should make every effort to follow the patient until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. Any adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with study procedures. If the outcome of pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 8.1. For reports of pregnancy in the female partner of a male patient, the EIU Reporting Form should be completed with the patient's enrollment number, initials, and date of birth, and details regarding the female partner should be entered.

15.0 ADMINISTRATIVE REQUIREMENTS

15.1. Good Clinical Practice

The study will be conducted in accordance with the international conference on harmonization (ICH) Guideline for GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the Investigator's Brochure.

15.2. Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. The sponsor will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or un-interpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

15.3. Electronic Case Report Form Completion

The sponsor or CRO designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for which they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information, and the date and time of the correction. The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he is responsible.

The sponsor, or a CRO designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

15.4. Study Monitoring

Monitoring and auditing procedures developed or approved by the sponsor will be followed, in order to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

15.5. Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent is to comply with ICH-GCP and all applicable regulatory requirement(s).

15.6. Subject Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.7. Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by the sponsor, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The sponsor, or a CRO designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact the sponsor, or a CRO designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

15.8. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IEC/IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.9. On-site Audits

Regulatory authorities, the IEC/IRB, and/or the sponsor may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

15.10. 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 patient, and amount returned to the sponsor, or a CRO designee, (or disposal of the drug, if approved by the sponsor) will be maintained by the clinical site. The sponsor 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.

15.11. Product Complaints

A product complaint is any dissatisfaction with a product which 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 the sponsor quality representative.

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

15.12. Adjudication Committee

An Adjudication Committee was established for the purpose of assessing hepatic safety and tolerability of the subjects. The Adjudication Committee meetings will be held to discuss subject safety as needed. Detailed procedures of the Adjudication Committee will be specified in the

Adjudication Committee Charter.

15.13. Closure of the Study

Within 90 days of the end of the study the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated, if in the opinion of the investigator or the sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or the sponsor by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or un-evaluable data
- Determination of a lack of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to the sponsor once the site's participation in the study has concluded.

Within 15 days of premature closure, the sponsor must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

15.14. Finance and Insurance

15.14.1. Finances

Prior to starting the study, the investigator and/or institution will sign a clinical study agreement with CRO. This agreement will include the financial information agreed upon by the parties.

15.14.2. Reimbursement, Indemnity, and Insurance

The sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

15.15. Record Retention

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 contained in the Trial Master File include:

- Subject files containing completed CRFs, informed consent forms, 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 EC/IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study 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

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and the sponsor must be notified.

16.0 ADDRESS LIST

Please refer to ATTACHMENT 5 for the address list of various stakeholders involved in this study.

17.0 PUBLICATION POLICY

All information regarding PLX3397 supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of PLX3397 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication. Therefore, the study site will have the opportunity to publish the results of the study, provided that Daiichi Sankyo 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 DS Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

18.0 REFERENCES

Beadling C, Jacobson-Dunlop E, Hodi FS, et al. KIT gene mutations and copy number in melanoma subtypes. Clin Cancer Res. 2008;14(21):6821-6828.

Carvajal RD, Antonescu CR, Wolchok JD. KIT as a therapeutic target in metastatic melanoma. JAMA. 2011;305(22):2327-2334.

Chapman PB, Hauschild A, Robert C. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507-2516.

Chi Z, Li S, Sheng X, Si L, et al. Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: A study of 522 consecutive cases. BMC Cancer. 2011;11:85.

Davies H, Bignell GR, Cox C. Mutations of the BRAF gene in human cancer. Nature. 2002;417(6892):949-954.

Guo J, Si L, Kong Y, Flaherty KT, Xu X, Zhu Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol. 2011;29(21):2904-2909.

Hao NB, Lü MH, Fan YH, et al. Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol. 2012;2012:948098.

Kong Y, Si L, Zhu Y, et al. Large-scale analysis of KIT aberrations in Chinese patients with melanoma. Clin Cancer Res 2011;17:1684-1691.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

PLX3397 Investigator's Brochure.

Si L, Guo J. C-kit-mutated melanomas: the Chinese experience. Curr Opin Oncol. 2013;25(2):160-165.

19.0 ATTACHMENT

ATTACHMENT 1: LABORATORY TESTS

Hematology

Hemoglobin and hematocrit	Platelet count
White blood cell count with differential	

Serum Chemistry

Sodium	Blood urea nitrogen (BUN)*	Total and direct bilirubin
Potassium	Creatinine (Creatinine clearance (CrCl)**)	Aspartate aminotransferase (AST)
Chloride	Uric acid	Alanine aminotransferase (ALT)
CO2	Total protein	Alkaline phosphatase (ALP)
Calcium	Albumin	Lactate dehydrogenase (LDH)
Phosphorus		Gamma glutamyl transferase (GGT)
Glucose		

*Urea to BUN conversions will be calculated using following formula (if need).

Urea (mmol/l) = BUN (mg/dl)* 0.357

**CrCl will be calculated using following formula (Cockcroft-Gault).

CrCl={((140–age) x weight (kg))/(72 x serum creatinine (mg/dl))} (x 0.85 if female)

Coagulation: PT/INR

Urinalysis

pH	Nitrites
Protein/albumin	Ketones/acetone
Glucose/sugar	Hemoglobin/blood
White blood cells (WBCs)	Casts or other microscopic findings

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

- The Screening serum pregnancy test must be negative within 7 days of initiating study drug.

Urine Pregnancy Test

- Urine pregnancy test per PI discretion, or institutional policy

Plasma Samples for PK

Blood Response Biomarkers

CSF-1, ctDNA

Biopsy Tissue Response Biomarkers

IHC for KIT, pERK, and Ki67

Tumor oncogene mutation sequencing

ATTACHMENT 2: LIST OF COMMON CYP3A INHIBITORS AND INDUCERS

Strong Inhibitors	Moderate inhibitors	Strong Inducers
• Boceprevir	• Aprepitant	• Carbamazepine
• Clarithromycin	• Cimetidine	• Enzalutamide
• Cobicistat	• Ciprofloxacin	• Mitotane
• Danoprevir and ritonavir	• Crizotinib	• Phenytoin
• Elvitegravir and ritonavir	• Cyclosporine	• Rifampin
• Grapefruit juice	• Dronedarone	• St. John's wort
• Idelalisib	• Erythromycin	
• Indinavir and ritonavir	• Fluconazole	
• Itraconazole	• Fluvoxamine	
• Ketoconazole	• Imatinib	
• Lopinavir and ritonavir	• Tofisopam	
• Nefazodone	• Verapamil	
• Nelfinavir		
• Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)		
• Posaconazole		
• Ritonavir		
• Saquinavir and ritonavir		
• Telithromycin		
• Tipranavir and ritonavir		
• Troleandomycin		
• Voriconazole		

Source: Food and Drug Administration (FDA) web site: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (3 Dec 2019). Available from: https://www fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

ATTACHMENT 3: RECIST V1.1 CRITERIA

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 one 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 patiented 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, <u>if not, the patient should be considered not evaluable from that point forward.</u>

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 one 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 complete response 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 complete response. 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 CA125 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 one 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 one measurable lesion is present at baseline all lesions up to a maximum of five 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 one or two organ sites involved a maximum of two (one site) and four lesions (two 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 x 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 case report form (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 one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

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 complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms 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 case report form:

- 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 BML (below measurable limit) 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 one 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 one 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 one 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 3 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 patient 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 patient's baseline lesions show partial or complete response. 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 patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient'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.

(18) F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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 patient'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-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one 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 19-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 19-2 is to be used.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient 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 patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one 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 patient is not evaluable. Similarly, if one 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 patient is known.

Table 19-1: Time Point Response: Patients with Targets (+/- Non-Target) Disease

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

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable

Table 19-2: 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*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable

a If a CR is truly met at the 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.

Table 19-3: Best Overall Response When Confirmation of CR and PR 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; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable

[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 patients with CR may not have a total sum of 'zero' on the case report form (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 patient with time point responses of PR-NE-PR as a confirmed response.

Patients 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 patients is to be determined by evaluation of target and non-target disease as shown in Table 19-1, Table 19-2, and Table 19-3.

Conditions that define 'early progression, early death and non-evaluability' 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 complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. 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.

ATTACHMENT 4: ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
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

* As published in Oken 1982.

ATTACHMENT 5: ADDRESS LIST

1. Sponsor

- **Medical Monitor**

!!!IP
211 Mount Ai.I Road, Basking Ridge, NJ 07920, US
[redacted]

- **Project Leader / Clinical Study Leader**

[redacted]
Asia Development Department, R&D Division, Daiichi Sankyo Co., Ltd,
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[redacted]

- **Delivery Lead**

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Asia Development Department, R&D Division, Daiichi Sankyo Co., Ltd,
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[redacted]

- **Data Management**

[redacted]

- **Biostatistician**

[redacted]

2. CRO

2.1. Hangzhou Tigermed Consulting Co., Ltd. (China and overall study coordination)

Floor 17 East, Baoyichuangyi Plaza, No.3760 Nanhuan Road, Binjiang District, Hangzhou,
Zhejiang Prov., 310053, P/R. China
[redacted]

[redacted]

- **CRO Project manager**

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Floor 17 East, Baoyichuangyi Plaza, No.3760 Nanhuan Road, Binjiang District, Hangzhou, Zhejiang Prov.,310053, P/R. China
[redacted]

2.2. DreamCIS (Korea study coordination)

l0F, Jeokseon H dai *BID,* 130, Sajik-ro, Jongno-gu, Seoul, Korea
[redacted]

- **Korea PM (Lead contact in Korea)**

[redacted]
10F, Jeokseon Hyndai *BID,* 130, Sajik-ro, Jongno-gu, Seoul, Korea
[redacted]

2.3. EDC Vendor

2.3.1. Medidata Solutions Inc.

350 Hudson Street, 9th Floor, New York, New York 10014, USA
[redacted]

2.4. Biological Specimens

2.4.1. COVANCE Inc. (Sample management, PK and PD assessment)

210 Carnegie Center, Princeton, NJ 08540-6233 USA

lllliiiiiion:

Global Study Manager, Global Project Management
Covance (Asia) Pte. Limited
1 International Business Park, #01-01 The Synergy, Singapore 609917
[redacted]
Covance Central Lab APAC contact Regional Study Coordinator
Covance Phaimaceutical Research and Development (Shanghai) Co. Limited
1st Floor, No. 6 Building, No. 151 Li Bing Road, Zhangjiang Hi-Tech Park, Shanghai 201203,

China
[redacted]

2.4.2. WuXi NextCODE (Shanghai) (Genomics)

#288 FuTe Zhong Road, Shanghai, China,
Contact erson:
[redacted]

2.4.3. Guardant Health (ctDNA)

505 Penobscot Dr, RedwoodCity, CA 94063, US
[redacted]

ATTACHMENT 6: VERSION 2.0 (AMENDMENT 1 SUMMARY OF CHANGES)

Note: Minor grammatical changes are not listed. Text inserted is shown in bold while text deleted is shown with strikethrough.

Section(s)	Previous	Amendment 1	Rationale
Title Page/Protocol Title; Signature Page, 4.0 Synopsis	Phase 2 Open Label, Multicenter Study of PLX3397 in Patients with Unresectable or Metastatic KIT-mutated Melanoma	Phase **1**/2 Open Label, Multicenter Study of PLX3397 in Patients with Unresectable or Metastatic KIT-mutated Melanoma	Due to lack of Phase 1 clinical data, modified the title to reflect the 2 portions of the study
4.0 Synopsis/Inclusion and Exclusion Criteria; 8.2 Exclusion Criteria	13. Active or chronic infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)	13. Active or chronic infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV). **Active or chronic HBV infection is defined as being HBsAg or HBV DNA-positive. Chronic HCV is defined as being anti-HCV or HCV RNA-positive.**	Clarification of definitions of HIV, HCV, and HBV-positive
4.0 Test Product, Dose, and Mode of Administration; 9.1 Study Drug Administration	PLX3397 will be supplied in 200 mg capsules and will be taken twice daily (BID) approximately 12 hours apart. Each dose is to be taken with approximately 8 ounces of water.	PLX3397 will be supplied in 200 mg capsules and will be taken twice daily (BID) approximately 12 hours apart. Each dose is to be taken with approximately ~~8 ounces~~ **200 mL** of water.	Clarification using relevant unit of measure
Table 4-1: Schedule of Events for Pilot Portion of Study, footnote #14	14. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (-3d), and at the End-of-Study visit (-3d) for patients enrolled in the Pilot portion of the study. A PET scan should be performed prior to biopsy collection procedures to avoid false positive results.	14. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (-3d), and at the End-of-Study visit (-3d) for patients enrolled in the Pilot portion of the study. **If a Screening tumor biopsy was obtained (Day -28 to Day -1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required.** A PET scan should be performed prior to biopsy collection procedures to avoid false positive results.	Added to clarify that if sufficient tissue is available from Screening biopsy, a second biopsy at Day 1 is not required.

Section(s)	Previous	Amendment 1	Rationale
Table 4-2: Schedule of Events for Phase 2 Portion of Study, footnote #13	13. Fresh tumor biopsy will be perfonned on Day 1 (-3d), Day 15 (-3d), and at the End-of-Study visit (-3d) for patients enrolled in the Pilot portion of the study. A PET scan should be perfo1med prior to biopsy collection procedures to avoid false positive results.	13. Fresh tumor biopsy will be perfonned on Day 1 (-3d), Day 15 (-3d), and at the End-of-Study visit (-3d) for patients enrolled in the Pilot portion of the study. If **a Screening tumo1· biop sy was obtain e d (Da y -28 to Da y -1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required.** A PET scan should be perf01med prior to biopsy collection procedures to avoid false positive results.	Added to clarify that if sufficient tissue is available from Screening biopsy, a second biopsy at Day 1 is not required.
5.1 Backgt"Ound	Apart from BRAF, KIT is the only other aben-ant signaling molecule for which targeted drugs are available. Some evidence of efficacy for imatinib in KIT advanced melanoma has been repo1ted in two Phase 2 trials (Jun et al. 2011)	Apart from BRAF, KIT is the only other aben-ant signaling molecule for which targeted dmgs are available. Some evidence of efficacy for imatinib in KIT advanced melanoma has been reported in two Phase 2 trials (JYB et al.Guo 2011)	Con-ected reference
7.1 Overview of Study Design	This Phase 2, open label, multicenter study includes a dose evaluation po1tion (Pilo t phase) in which the safety profile of PLX3397 as a single oral agent will be evaluated, followed by an expansion cohort (Phase 2) in which the efficacy and safety of PLX3397 administered at the recommended Phase 2 dose (RP2D). ..	This Phase 1/2, open label, multicenter study includes a dose evaluation p01tion (Pilot phase) in which the safety profile of PLX3397 as a single oral agent will be evaluated, followed by an expansion coho1t (Pha se 2) in which the efficacy and safety of PLX3397 administered at the recommended Phase 2 dose (RP2D).. .	Due to lack of Phase 1 clinical data, modified the study design description to reflect the 2 portions of the study
10.1 Study Personnel and Organizations, SAE Reporting Contact	The inves tigator will ensure that the SAE repo1ting form is completed and E-mailed/eFaxed to the following address with.in 24 hour s of learning of the occulTence of any SAE: [redacted] US **fax number:** [redacted]	The investigator will ensure that the SAE rep01t ing fonn is completed and E-mailed/eFaxed to the following address v.rithin 24 hour s of learning of the occulTence of any SAE : **Na me: SynteractHCR Safety SAE Facsimile** **Phone:** [redacted]	Updated to reflect CUil'ent SAE reporting contact

Section(s)	Previous	Amendment 1	Rationale
10.2 Arrangements for Recruitment of Subjects	Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB) and/or independent ethics committee (IEC).	Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB) and/or independent ethics committee (IEC). **Subjects will be compensated for their participation in this study.**	Added for clarity

ATTACHMENT 7: VERSION 3.0 (AMENDMENT 2 SUMMARY OF CHANGES)

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes. Text inserted is shown in bold while text deleted is shown with strikethrough.

Section(s)	Previous	Amendment 2	Rationale
Title Page	IND Number: TBD Eudra CT Number: TBD	~~IND Number: TBD~~ ~~Eudra CT Number: TBD~~	To reflect that the protocol will not have an IND or Eudra CT Number.
Protocol Synopsis – Objectives; Section 6.3 Exploratory Objectives; Section 11.1.7 Cycle 2, Day 1 (Pilot Portion); Section 11.2.7 Cycle 2, Day 1 (Phase II); Section 11.3.4 Study Procedures	To evaluate tumor response by PET scan on Day 15 compared to Baseline (Pilot portion of the study)	To evaluate tumor response by PET scan on ~~Day 15~~ **Day 1 of Cycle 2** compared to Baseline (Pilot portion **and first 13 patients of the Phase II portion** of the study)	To include PET scans for the first 13 patients enrolled in the phase II portion of the study.
Protocol Synopsis – Number of Patients; Section 7.2 Number of Subjects	Pilot: Up to 12 patients	Pilot: ~~Up to~~ **Approximately 6-**12 patients	To more accurately reflect planned study schema.
Protocol Synopsis, Study Procedures; Section 11.3.3 Study Procedures	Fresh tumor tissue for the purpose of exploratory pharmacodynamics as well as PET scan will be obtained at baseline (Day 1) and Day 15 of Cycle 1 in patients of the Phase 1 portion.	Fresh tumor tissue for the purpose of exploratory pharmacodynamics **will be obtained at baseline (Day 1) and optionally also at Day 15 of Cycle 1 and End-of-treatment in the Pilot portion and first 13 patients of the Phase II portion.** ~~as well as~~ PET scan will be obtained at baseline (Day 1) and ~~Day 15 of Cycle 1~~ **Day 1 of Cycle 2** ~~in patients of the Phase 1 portion~~ **in the Pilot portion and first 13 patients of the Phase II portion.**	To indicate that fresh tumor tissue biopsy is optional at Cycle 1 Day 15 and End-of-treatment and to specify that the first 13 subjects enrolled in the Phase II portion and on Pilot portion will have a PET scan and Fresh Tumor Biopsy

Section(s)	Previous	Amendment 2	Rationale
Protocol Synopsis – PK Parameters	The pharmacokinetic profile of plasma PLX3397 will be analyzed by measuring area under the plasma concentration–time curve ($AUC_{0\text{-}6}$, $AUC_{0\text{-}\infty}$), peak concentration (C_{max}), time to peak concentration (T_{max}), half-life ($T_{½}$), and terminal elimination rate constant (Kel). Dose proportionality following study dosing will be explored by analyzing natural log-transformed pharmacokinetic variables, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate. Dose linearity for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} will also be explored by a linear model.	The pharmacokinetic profile of plasma PLX3397 will be analyzed by measuring area under the plasma concentration–time curve ($AUC_{0\text{-}6}$, $AUC_{0\text{-}\infty}$), peak concentration (C_{max}), time to peak concentration (Tmax), **and** half-life ($T_{½}$)**.** ~~, and terminal elimination rate constant (Kel).~~ ~~Dose proportionality following study dosing will be explored by analyzing natural log transformed pharmacokinetic variables, AUC0 t, AUC0 ∞, and Cmax, with a linear model including the natural log transformed dose as a covariate. Dose linearity for AUC0 t, AUC0 ∞, and Cmax will also be explored by a linear model.~~	To make consistent with Section 13.1.8.1 Pharmacokinetic Analysis
Protocol Synopsis – PD Parameters	Histological/molecular analysis of paired fresh tumor biopsy, and positron emission tomography (PET) scan evaluation on Day 15 compared to Baseline in the first 13 patients in the Phase 2 portion of the study will be performed. Exploratory tissue studies will include IHC for KIT, pERK, Ki67 and other markers of target or tumor evaluation. Exploratory blood studies in the Phase 2 portion of the study will measure CSF-1 and other markers of target inhibition and tumor evaluation.	Histological/molecular analysis of paired fresh tumor biopsy, and positron emission tomography (PET) scan evaluation on ~~Day 15~~ **Day 1 of Cycle 2** compared to Baseline in the first 13 patients in the Phase ~~2~~**II** portion of the study will be performed. Exploratory tissue studies will include IHC for KIT, pERK, Ki67 and other markers of target or tumor evaluation. Exploratory blood studies in the Phase ~~2~~**II** portion of the study will measure CSF-1 ~~and other markers of target inhibition and tumor evaluation~~.	To make consistent with rest of protocol.

Section(s)	Previous	Amendment 2	Rationale
Protocol Synopsis – Endpoints; **Section 12.1 Pilot Portion;** **Section 12.2 Phase II**	The endpoints in the Pilot portion of the study include: … • Serum/plasma tumor biomarkers include but not limited to CSF-1, and whole blood CD14/16 mononuclear cell counts The exploratory endpoints in the Pilot portion of the study include: • Immunohistochemistry and molecular analysis of paired fresh tumor biopsy • Positron emission tomography (PET) scan evaluation on Day 15 compared to Baseline … The exploratory endpoints in the Phase 2 portion of the study include: • Serum/plasma tumor biomarkers including but not limited to CSF-1, whole blood CD14/16 mononuclear cell counts	The endpoints in the Pilot portion of the study include: … • Serum/plasma tumor biomarkers ~~include but not limited to~~ **including** CSF-1~~, and whole blood CD14/16 mononuclear cell counts~~ The exploratory endpoints in the Pilot portion of the study include: • Immunohistochemistry and molecular analysis of **archival and** paired fresh tumor biopsy • Positron emission tomography (PET) scan evaluation on ~~Day 15~~ **Day 1 of Cycle 2** compared to Baseline … The exploratory endpoints in the Phase ~~2~~**II** portion of the study include: • **Immunohistochemistry and molecular analysis of archival and paired fresh tumor biopsy** • Serum/plasma tumor biomarkers including ~~but not limited to~~ CSF-1~~, whole blood CD14/16 mononuclear cell counts~~ • **Positron emission tomography (PET) scan evaluation on Day 1 of Cycle 2 compared to Baseline**	To reflect that CD14/16 testing is not found to be operationally feasible. To make consistent with rest of protocol. To make consistent with rest of protocol.
Table 4-1: Schedule of Events for Pilot Portion of Study	N/A N/A **PET scan – Cycle 1 Day 15**	**Archival tissue – Screening** **Blood sampling for PD – Cycle 1 Day 1 and Day 15** **PET scan – Cycle 2 Day 1**	To add archival tissue collection at screening. To make consistent with study endpoints. To spread study procedures apart for patient convenience.

Section(s)	Previous	Amendment 2	Rationale
Table 4-1: Schedule of Events for Pilot Portion of Study (footnotes)	Footnote 5. Qualified KIT mutation(s) must be documented prior to enrollment (see Table 11-1).	Footnote 5. ~~Qualified~~ **Documentation of** KIT mutation(s) ~~must be documented~~ prior to enrollment ~~(see Table 11-1)~~ **to include submission of deidentified sequencing report and associated .scf output files**.	To clarify documentation required based on discussion with investigators.
	Footnote 13. PET scan will be performed on at Screening (-3d) and Day 15 (-3d) of Cycle 1 for patients enrolled in the Pilot portion of the study.	Footnote 13. PET scan will be performed ~~on~~ at ~~Screening~~ **Day 1** (-3d) and ~~Day 15~~ **Day 1** (-3d) of Cycle ~~1~~ **2** for patients enrolled in the Pilot portion of the study.	To make consistent with study endpoints.
	Footnote 14. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (-3d), and at the End-of-Study visit (-3d) for subjects enrolled in the Pilot portion of the study. If a Screening tumor biopsy was obtained (Day -28 to Day -1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required. A PET scan should be performed prior to biopsy collection procedures to avoid false positive results.	Footnote 14. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (-3d) **(optional)**, and at the End-of-Study visit (-3d) **(optional)** for subjects enrolled in the Pilot portion of the study. **Biopsies must be core needle or excisional (not fine needle), and sufficient for 20 unstained slides of 4-5 micron thickness.** If a Screening tumor biopsy was obtained (Day -28 to Day -1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required. ~~A~~ **All** PET scan**s** should be performed prior to biopsy collection procedures to avoid false positive results.	To specify the sampling requirements for biopsies and indicate that fresh tumor biopsies are optional at Cycle 1 Day 15 and End-of-Study.
	N/A	Footnote 15. Availability of archival tissue should be documented and at least 10 unstained slides of 5 micron thickness should be submitted to the central lab.	To specify procedure for collecting archival tissue.
	N/A	**Footnote 16. On Day 1 and Day 15 of Cycle 1 during the Pilot portion of the study, blood samples for pharmacodynamics (PD) analysis will be obtained pre-morning dose.**	To make consistent with study endpoints.
Table 4-2: Schedule of Events for Phase II Portion of Study	N/A	**Archival tissue - Screening**	To add archival tissue collection at screening.
	N/A	**PET Scan – Cycle 1 Day 1, Cycle 2 Day 1**	To make consistent with study endpoints.

Section(s)	Previous	Amendment 2	Rationale
Table 4-2: Schedule of Events for Phase II Portion of Study (footnotes)	Footnote 5. Qualified KIT mutation(s) must be documented prior to enrollment (see Table 11-1).	Footnote 5. ~~Qualified~~ **Documentation of** KIT mutation(s) ~~must be documented~~ prior to enrollment ~~(see Table 11-1)~~ **to include submission of deidentified sequencing report and associated .scf output files**.	To clarify documentation required based on discussion with investigators.
	Footnote 13. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (-3d), and at the End-of-Study visit (-3d) for first 13 patients enrolled in Phase 2. If a Screening tumor biopsy was obtained (Day 28 to Day 1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required. A PET scan should be performed prior to biopsy collection procedures to avoid false positive results.	Footnote 13. Fresh tumor biopsy will be performed on Day 1 (-3d), Day 15 (-3d) **(optional)**, and at the End-of-Study visit (-3d) **(optional)** for first 13 patents subjects enrolled in Phase II. **Biopsies must be core needle or excisional (not fine needle), and sufficient for 20 unstained slides of 4-5 micron thickness.** If a Screening tumor biopsy was obtained (Day -28 to Day -1), and there was sufficient tissue from that sample for laboratory testing, then tumor biopsy on Day 1 is not required. ~~A~~ **All** PET scan**s** should be performed prior to biopsy collection procedures to avoid false positive results.	To specify the sampling requirements for biopsies and indicate that fresh tumor biopsies are optional at Cycle 1 Day 15 and End-of-Study.
	N/A	**Footnote 14. Availability of archival tissue should be documented and at least 10 unstained slides of 5 micron thickness should be submitted to the central lab.**	To specify procedure for collecting archival tissue.
	N/A	**Footnote 15. PET scan will be performed at Day 1 (-3d) of Cycle 1 and Day 1 (-3d) of Cycle 2 for the first 13 patients enrolled in the Phase II portion of the study..**	To make consistent with study endpoints.
Section 9.2.1 Dose Evaluation	Cohort 2 will be carried out only if Cohort 1 is considered intolerable. Study treatment may be delayed up to 2 weeks to permit resolution of any treatment-related toxicity outside the DLT window.	Cohort ~~2~~ **-1** will be carried out only if Cohort 1 is considered intolerable. Study treatment may be delayed up to 2 weeks to permit resolution of any treatment-related toxicity outside the DLT window.	To make consistent with the dose cohort levels.

Section(s)	Previous	Amendment 2	Rationale
Section 9.3 Dose Escalation Rules	9.3 Dose Escalation Rules Dose escalation will occur in accordance with the rules listed below. … • After dosing has been completed in each cohort, safety and PK data (as applicable) will be reviewed by and dose escalation decisions made by the Sponsor, and investigators and study staff from all participating sites.	9.3 Dose ~~Escalation~~ **Reduction** Rules Dose ~~escalation~~ **reduction** will occur in accordance with the rules listed below. … • After dosing has been completed in each cohort, safety and PK data (as applicable) will be reviewed by and dose ~~escalation~~ **reduction** decisions made by the Sponsor, and investigators and study staff from all participating sites.	To make language consistent with study schema.
Section 9.4 Definitions of Dose-Limiting Toxicity	In the Pilot portion of the study, DLTs will be assessed during a DLT assessment window of 28 days in Cycle 1. However, if clinically relevant ≥Grade 3 cumulative toxicities are observed beyond Cycle 1, these should also be taken into account when assessing further dose escalation. … If, for any reason, either the Sponsor or principal investigator deems further dose escalation inappropriate. Final decisions on determination of DLTs will be made in consultation between the Sponsor and the principal investigator.	In the Pilot portion of the study, DLTs will be assessed during a DLT assessment window of 28 days in Cycle 1. However, if clinically relevant ≥Grade 3 cumulative toxicities are observed beyond Cycle 1, these should also be taken into account when assessing further dose ~~escalation~~ **reduction**. … If, for any reason, either the Sponsor or principal investigator deems further dose ~~escalation~~ **reduction** inappropriate. Final decisions on determination of DLTs will be made in consultation between the Sponsor and the principal investigator.	To make language consistent with study schema.
Table 9-1: Recommended PLX3397 Dose Modifications **– Grade 3 or 4 Neutropenia** **– Grade 4 Thrombocytopenia**	If not recovered to ANC ≥1 X 109/L after 7 days, reduce dose by 1 dose level If not recovered to ANC ≥1 X 109/L after 7 days, reduce dose by 2 dose levels. If not recovered to PLT ≥75 x 109/L after 7 days, reduce dose by 2 dose levels.	If not recovered to ANC ≥1 X 109/L after 7 days, reduce dose by 1 dose level **(200 mg).** If not recovered to ANC ≥1 X 109/L after 7 days, reduce dose by ~~2 dose levels~~ **an additional dose level (200 mg)**. If not recovered to PLT ≥75 x 109/L after 7 days, reduce dose by **an additional** ~~2~~ dose level~~s~~.	To specify the dose level reduction of 200 mg. To specify the additional dose level reduction at the 2nd appearance of Grade 3 or 4 Neutropenia. To specify the additional dose level reduction at the 2nd appearance of Grade 4 Thrombocytopenia.

Section(s)	Previous	Amendment 2	Rationale
Section 9.6 Stopping Rules	The Pilot and Phase 2 portions of the study may be discontinued if the study is terminated by the Sponsor, the Food and Drug Administration (FDA) or the China Food and Drug Administration (CFDA), or other regulatory authorities.	The Pilot and Phase ~~2~~ **II** portions of the study may be discontinued if the study is terminated by the Sponsor, ~~the Food and Drug Administration (FDA) or~~ the China Food and Drug Administration (CFDA), or other regulatory authorities.	To reflect that the protocol will not be conducted under a FDA IND.
Section 9.13 Storage, Handling, and Accountability	All unused and partially used Study drug must be sealed and returned to the Principal Investigator or his/her designee, or destroyed on Site in accordance with the established procedures for drug destruction, and with approval by the Principal Investigator or his/her designee.	All unused and partially used Study drug must be sealed and returned to the ~~Principal Investigator or his/her designee~~ **Sponsor**, or destroyed on Site in accordance with the established procedures for drug destruction, and with approval by the Principal Investigator or his/her designee.	To clarify Study drug handling procedures.
Section 11.1.1 Screening Visit (Day -28 to Day -1)	N/A	• Documentation of archival tissue availability	To add archival tissue collection at screening.
Section 11.1.3 Cycle 1, Day 1	N/A	• Blood sampling for PD analysis	To make consistent with study endpoints.
Section 11.1.5 Cycle 1, Day 15	N/A • Fresh tumor biopsy (may be performed within 3 days prior to the study visit) • PET scan (–3-day window)	• Blood sampling for PD analysis • Fresh tumor biopsy (**optional, and** may be performed within 3 days prior to the study visit) • ~~PET scan (3 day window)~~ [moved to Cycle 2 Day 1]	To make consistent with study endpoints. To spread study procedures apart for patient convenience.
Section 11.1.7 Cycle 2, Day 1 ± 3 days;	N/A On this day, the patient will take the morning and evening does of study medication with food. N/A	• PET scan (–3-day window) [moved from Cycle 1 Day 15] ~~On this day, the patient will take the morning and evening does of study medication with food.~~ **Procedures to be performed *after* the morning dose:** • **12-lead ECG (2 hours post-dose)**	To spread study procedures apart for patient convenience. To make consistent with Section 9.1 Study Drug Administration. To make consistent with the Schedule of Events.
Section 11.2.1 Screening Visit (Day -28 to Day -1)	N/A	• Documentation of archival tissue availability	To add archival tissue collection at screening.

Section(s)	Previous	Amendment 2	Rationale
Section 11.2.3 Cycle 1, Day 1	N/A	• PET scan (–3-day window)	To make consistent with study endpoints.
Section 11.2.4 Cycle 1, Day 8 ± 3 days	Urinalysis, including PH, protein/albumin, glucose, nitrates, ketones/acetones, and hemoglobin/blood	~~Urinalysis, including PH, protein/albumin, glucose, nitrates, ketones/acetones, and hemoglobin/blood~~	To make consistent with the Schedule of Events.
Section 11.2.5 Cycle 1, Day 15 ± 3 days	• Fresh tumor biopsy (first 13 patients enrolled in Phase 2; –3-day window) N/A	• Fresh tumor biopsy (**optional,** first 13 patients enrolled in Phase ~~2~~**II**; –3-day window) **Procedures to be performed *after* the morning dose:** **12-lead ECG (2 hours post-dose)**	To make consistent with the Schedule of Events.
Section 11.2.7 Cycle 2, Day 1 ±3 days	On this day, the patient will take the morning and evening does of study medication with food. N/A N/A	~~On this day, the patient will take the morning and evening does of study medication with food.~~ • PET scan (–3-day window) [moved from Cycle 1 Day 15] **Procedures to be performed *after* the morning dose:** • **12-lead ECG (2 hours post-dose)**	To make consistent with Section 9.1 Study Drug Administration. To spread study procedures apart for patient convenience. To make consistent with the Schedule of Events.
Section 11.2.10 End-of-Study Visit	• Fresh tumor biopsy (first 13 patients enrolled in Phase 2; –3-day window) Urinalysis, including PH, protein/albumin, glucose, nitrates, ketones/acetones, and hemoglobin/blood	• Fresh tumor biopsy (**optional,** first 13 patients enrolled in Phase ~~2~~**II**; –3-day window) ~~Urinalysis, including PH, protein/albumin, glucose, nitrates, ketones/acetones, and hemoglobin/blood~~	To make consistent with the Schedule of Events.
Section 11.3.3 Fresh Tissue Biopsy Samples (Pilot Portion and First 13 Patients of Phase II Portion of the Study)	A pre-dose tumor biopsy of a progressive lesion will be obtained in patients with accessible tissue. Paraffin-fixed tissue slides will be collected and stored for subsequent evaluation using a project-specific companion diagnostic assay to be performed at one or more central laboratories. Biopsy tissues will interrogated for biomarkers of KIT mutation.	A pre-dose tumor biopsy of a progressive lesion will be obtained in patients with accessible tissue. Paraffin-fixed tissue slides will be collected and stored for subsequent evaluation using ~~a~~ project-specific ~~companion diagnostic assay~~ **tumor assays** to be performed at one or more central laboratories. ~~Biopsy tissues will interrogated for biomarkers of KIT mutation.~~	To specify the type of assay that will be performed on fresh tissue Biopsy.

Section(s)	Previous	Amendment 2	Rationale
Section 11.3.4 PET Scans (Pilot Portion and First 13 Patients of Phase II Portion of the Study)	^{18}FDG-PET scans will be obtained during Screening and Day 1 and at Day 15 of Cycle 1.	^{18}FDG-PET scans will be obtained **at Cycle 1** ~~during Screening and~~ Day 1 and at **Cycle 2 Day 1**~~Day 15 of Cycle 1~~.	To specify the timepoint for the PET scan.
Section 13.1.7 Efficacy Analysis	Thirteen patients will be enrolled in the first stage, with at least two responses required to proceed to the second stage. Eight responses among 29 patients are required for PLX3397 to be considered promising.	Thirteen patients will be enrolled in the first stage, with at least three~~wo~~ responses required to proceed to the second stage. Eight responses among 29 patients are required for PLX3397 to be considered promising. **See Section 13.1.10 for discussion of interim analysis.**	To add reference to discussion of interim analysis plan.
Section 13.1.8.3 Tissue Evaluation	Exploratory tissue studies will include IHC for KIT, pERK, Ki67 and other markers of target or tumor evaluation. Tissue may also be used for KIT or other oncogene mutation sequencing confirmation. Blood biomarker analysis Exploratory studies in the Phase 2 part of the study will measure CSF-1 and other markers of target inhibition and tumor evaluation. Planned biomarkers are listed in Attachment 1.Safety Analysis	Exploratory tissue studies will include IHC for KIT, pERK, Ki67 ~~and other markers of target or tumor evaluation~~. Tissue may also be used for KIT or other oncogene mutation sequencing confirmation. ~~Blood biomarker analysis~~ Exploratory studies in the Phase ~~2~~**II** part of the study will measure CSF-1 ~~and other markers of target inhibition and tumor evaluation.~~ Planned biomarkers are listed in Attachment 1.Safety Analysis	To specify the target biomarkers.
Section 13.1.10 Interim Analysis	No formal interim analysis is planned.	~~No formal interim analysis is planned.~~ **The Phase II portion of the study will follow a Simon two-stage design to compare a null ORR of 15% with an alternative ORR of 40% with 90% power and a one-sided type I error of 5%. The total sample size will be 29 evaluable patients. Thirteen patients will be enrolled in the first stage before triggering an interim analysis. At least three responses are required to proceed to the second stage. Eight responses among 29 patients are required for PLX3397 to be considered promising.**	To specify the interim analysis plans for the study.

Section(s)	Previous	Amendment 2	Rationale
Section 15.1.1 Adverse Event Definition	This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug. An AE includes, but is not limited to, the following…	This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug. **Clear progression of the underlying cancer and hospitalizations due to the progression of cancer should not be reported as an adverse event, or a serious adverse event**. An AE includes, but is not limited to, the following…	To further clarify the definition of the reportability of an adverse event.
Section 15.2.1 Studies Conducted Within the European Community	**Section 15.2.1 Studies Conducted Within the European Community** In accordance with the European Clinical Trial Directive (Directive 2001/20/EC), suspected, unexpected serious adverse reactions (SUSARs) associated with the use of any study drug (Plexxikon and non-Plexxikon) will be processed with the following responsibilities. Plexxikon (or its agent) will notify, in an expedited manner, the appropriate competent authorities, the IEC, and the reporting investigator of the SUSARs for all Plexxikon sponsored studies. In addition, Plexxikon (or its agent) will send out a monthly line-listing of all SUSAR associated with study drug(s) to the IECs, all investigators, and all competent authorities for member states where the studies are being conducted.	~~**Section 15.2.1 Studies Conducted Within the European Community**~~ ~~In accordance with the European Clinical Trial Directive (Directive 2001/20/EC), suspected, unexpected serious adverse reactions (SUSARs) associated with the use of any study drug (Plexxikon and non-Plexxikon) will be processed with the following responsibilities.~~ ~~Plexxikon (or its agent) will notify, in an expedited manner, the appropriate competent authorities, the IEC, and the reporting investigator of the SUSARs for all Plexxikon sponsored studies. In addition, Plexxikon (or its agent) will send out a monthly line listing of all SUSAR associated with study drug(s) to the IECs, all investigators, and all competent authorities for member states where the studies are being conducted.~~	To remove the section 15.2.1 as this protocol will not be conducted in the EU.
Section 16.12 Closure of the Study	Determination of efficacy based on interim analysis	Determination of **a lack of** efficacy based on interim analysis	To clarify closure of study rules.

Section(s)	Previous	Amendment 2	Rationale
ATTACHMENT 1: LABORATORY TESTS	Blood Response Biomarkers Paired Biopsy Tissue Response Biomarkers pERK and Ki67 RNA sequencing Other response or resistance biomarkers as appropriate Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, the definitive list of analyses remains to be determined, and may include additional markers of macrophage activity, in addition to anti-tumor biomarkers that may be related to PLX3997 treatment.	Blood Response Biomarkers **CSF-1** ~~Paired~~ Biopsy Tissue Response Biomarkers **KIT,** pERK**,** and Ki67 ~~RNA~~ **Tumor oncogene mutation** sequencing ~~Other response or resistance biomarkers as appropriate~~ ~~Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, the definitive list of analyses remains to be determined, and may include additional markers of macrophage activity, in addition to anti tumor biomarkers that may be related to PLX3997 treatment.~~	To specify the target biomarkers in biopsy tissue and blood samples.

ATTACHMENT 8: VERSION 4.0 (AMENDMENT 3 SUMMARY OF CHANGES)

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes. Text inserted is shown in bold while text deleted is shown with strikethrough.

Section(s)	Previous	Amendment 3	Rationale
Protocol Synopsis; Section 9.4 Definitions of Dose-Limiting Toxicity	• Any Grade ≥3 hematologic toxicity except: • Grade 3 lymphopenia • Grade 3 neutropenia ≤7 days • Any thrombocytopenia resulting in clinically significant bleeding • Any Grade ≥3 non-hematologic toxicity except: • Nausea, vomiting, and/or diarrhea of Grade 3 severity that resolves within 7 days with optimal prophylaxis and/or treatment. … • If, for any reason, either the Sponsor or principal investigator deems further dose escalation inappropriate. Final decisions on determination of DLTs will be made in consultation between the Sponsor and the principal investigator	• Any Grade ≥3 **clinically significant** hematologic toxicity except: • Grade 3 lymphopenia • Grade 3 neutropenia ≤7 days • Any thrombocytopenia resulting in clinically significant bleeding • Any Grade ≥3 **clinically significant** non-hematologic toxicity except: • Nausea, vomiting, and/or diarrhea of Grade 3 severity that resolves within 7 days with optimal prophylaxis and/or treatment. … • If, for any reason, either the Sponsor or principal investigator deems further dose **reduction-** ~~escalation~~ inappropriate. Final decisions on determination of DLTs will be made in consultation between the Sponsor and the principal investigator. • **For the purposes of determining the DLT in Cycle 1, the use of G-CSF or other hematologic growth factors is not permitted during Cycle 1. If a patient develops a protocol defined hematologic DLT and requires the use of G-CSF or other hematologic growth factors, they may be used in accordance with local standard of care, and per Section 9.7.**	To clarify DLT definition and include rules on G-CSF use during the DLT period.

Section(s)	Previous	Amendment 3	Rationale
Protocol Synopsis; Section 9.6 Stopping Rules	The Pilot and Phase II portions of the study may be discontinued if the study is terminated by the Sponsor, the Food and Drug Administration (FDA) or the China Food and Drug Administration (CFDA), or other regulatory authorities.	The Pilot and Phase II portions of the study may be discontinued if the study is terminated by the Sponsor, ~~the Food and Drug Administration (FDA) or~~ the China Food and Drug Administration (CFDA), or other regulatory authorities.	To make consistent with study region.
Table 9-1: Recommended PLX3397 Dose Modifications – Grade 3 or 4 Neutropenia	1st appearance: If not recovered to ANC ≥1 X 10^9/L after 7 days, reduce dose by 1 dose level (200 mg). 2nd appearance: If recovered to ANC ≥1 X 10^9/L in ≤7 days, reduce dose by 1 dose level. If not recovered to ANC ≥1 X 10^9/L after 7 days, reduce dose by an additional dose level (200 mg). 3rd appearance: If recovered to ANC ≥1 X 10^9/L in ≤7 days, reduce dose by 1 dose level.	1st appearance: If not recovered to ANC ≥1 X 10^9/L after 7 days, reduce dose by ~~1 dose level (~~200 mg~~)~~. 2nd appearance: If recovered to ANC ≥1 X 10^9/L in ≤7 days, reduce dose by ~~1 dose level~~ **200 mg**. If not recovered to ANC ≥1 X 10^9/L after 7 days, reduce dose by an additional ~~dose level (~~200 mg~~)~~. 3rd appearance: If recovered to ANC ≥1 X 10^9/L in ≤7 days, reduce dose by ~~1 dose level~~ **200 mg**.	To specify the dose level reductions of 200 mg.
Table 9-1: Recommended PLX3397 Dose Modifications – Grade 3 or 4 Febrile Neutropenia	1st appearance: If recovered to ANC ≥1 X 10^9/L and T ≤38°C in ≤ 7 days, reduce dose by 1 dose level. 2nd appearance: If recovered to ANC ≥1 X 10^9/L and T ≤38°C, reduce dose by an additional 1 dose level.	1st appearance: If recovered to ANC ≥1 X 10^9/L and T ≤38°C in ≤ 7 days, reduce dose by ~~1 dose level~~ **200 mg**. 2nd appearance: If recovered to ANC ≥1 X 10^9/L and T ≤38°C, reduce dose by an additional ~~1 dose level~~ **200 mg**.	To specify the dose level reductions of 200 mg.

Section(s)	Previous	Amendment 3	Rationale
Table 9-1: Recommended PLX3397 Dose Modifications – Grade 4 Thrombocytopenia	1st appearance: If not recovered to PLT ≥75 x 10^9/L after 7 days, reduce dose by 1 dose level. 2nd appearance: If recovered to PLT ≥75 x 10^9/L in ≤7 days, reduce dose by 1 dose level. If not recovered to PLT ≥75 x 10^9/L after 7 days, reduce dose by an additional dose level. 3rd appearance: If recovered to PLT ≥75 x 10^9/L in ≤7 days, reduce dose by 1 dose level.	1st appearance: If not recovered to PLT ≥75 x 10^9/L after 7 days, reduce dose by ~~1 dose level~~ **200 mg**. 2nd appearance: If recovered to PLT ≥75 x 10^9/L in ≤7 days, reduce dose by ~~1 dose level~~ **200 mg**. If not recovered to PLT ≥75 x 10^9/L after 7 days, reduce dose by an additional ~~dose level~~ **200 mg**. 3rd appearance: If recovered to PLT ≥75 x 10^9/L in ≤7 days, reduce dose by ~~1 dose level~~ **200 mg**.	To specify the dose level reductions of 200 mg.
Table 9-1: Recommended PLX3397 Dose Modifications – Non-Hematologic Grade 3 (excluding transaminase increases)	1st appearance: If symptoms persist for >5 days despite supportive management, reduce by 1 dose level. 2nd appearance: If recovered <5 days, reduce dose by 1 dose level.	1st appearance: If symptoms persist for >5 days despite supportive management, reduce by ~~1 dose level~~ **200 mg**. 2nd appearance: If recovered <5 days, reduce dose by ~~1 dose level~~ **200 mg**.	To specify the dose level reductions of 200 mg.
Table 9-1: Recommended PLX3397 Dose Modifications – Non-Hematologic Grade 4 (excluding transaminase increases)	1st appearance: If recovered <5 days, reduce dose by 1 dose level.	1st appearance: If recovered <5 days, reduce dose by ~~1 dose level~~ **200 mg**.	To specify the dose level reductions of 200 mg.
Section 9.7 Concomitant Medications (and Procedures)	N/A	**For the purposes of determining the DLT in Cycle 1, the use of G-CSF or other hematologic growth factors is not permitted during Cycle 1. If a patient develops a protocol defined hematologic DLT and requires the use of G-CSF or other hematologic growth factors, they may be used in accordance with local standard of care.**	To define G-CSF use on study.

Section(s)	Previous	Amendment 3	Rationale
Section 10.1 Study Personnel and Organizations	Medical Monitor: (Emergency Contacts) Chief Medical Officer [redacted] Plexxikon Inc. 91 Bolivar Drive, Berkeley, CA **11710** Phone: [redacted]	[redacted] Medical Monitor (Emergency Contacts) **Vice President, Oncology ~~Chief Medical Officer~~** Plexxikon Inc. 91 Bolivar Drive, Berkeley, CA 94710 Phone: [redacted]	To update the Medical Monitor contact.
Section 11.1.3 Cycle 1, Day 1	Se1umche1nistry, including sodium, potassium, chloride, CO2, calcium, phosphoms, glucose, BUN, creatinine, uric acid, total protein, albumin, total and direct bilimbin, AST, ALT, alkaline phosphatase, LDH, and PT/INR	Senun chemistry, including sodium, potassium, chloride, CO2, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total protein, albmnin, total and direct bilimbin, AST, ALT, alkaline phosphatase, **and** LDH, **ana PT'DT-R**	To make consistent with Schedule of Events.
Section 11.2.10 End-of-Study Visit	The End-of-Study visit is scheduled within the 28-day period after the last dose of study dmg or before sta1t ing any new anti-neoplastic therapy.	The End-of-Study visit is scheduled within the 28-day period after the last dose of study dmg **and** el' before sta1ting any new anti-neoplastic therapy.	To make consistent with Protocol Synopsis.

ATTACHMENT 9: VERSION 5.0 (AMENDMENT 4 SUMMARY OF CHANGES)

- Inclusion criteria added to define prior cancer history treatment.
  Rationale: To clarify the eligible study population.
- Inclusion criteria for adequate organ and bone marrow function clarified.
  Rationale: To further define eligible lab values.
- Exclusion criteria amended for required washout period before starting on study to include chemotherapy, antibody or antibody drug conjugate, small molecule TKI, immunotherapy, investigational drug, or radiation therapy.
  Rationale: To clarify the eligible study population.
- Exclusion criteria for resolution of adverse effects from prior treatment amended.
  Rationale: To more clearly define parameters of unresolved adverse effects for study eligibility.
- Exclusion criteria for history of another malignancy amended.
  Rationale: To more clearly define parameters of prior cancer history for study eligibility.
- Dose-limiting toxicity (DLT) criteria amended to indicate that Grade 3 nausea, vomiting, and/or diarrhea that resolves to Grade $\leq$2 within 7 days will not be considered a DLT.
  Rationale: To clarify the rule regarding the resolution of Grade 3 nausea, vomiting, and/or diarrhea for purposes of a DLT determination.
- Dose-limiting toxicity (DLT) rule added to include that any dose reduction required during Cycle 1 due to potential toxicity is a DLT.
  Rationale: To clarify that any dose reduction during the DLT period is considered a DLT.
- Additional study assessments were added to the Schedule of Events for Pilot and Phase II Portions of Study (Table 4-1 and Table 4-2 at Cycle 2 Day 8, Cycle 2 Day 15, and Cycle 2 Day 22) to obtain hematology, serum hematology, and additional safety assessments.
  Rationale: To increase monitoring of liver function and safety during the first 8 weeks of PLX3397 therapy due to updated safety information.
- Assessments on Cycle 2 Day 8 and Cycle 2 Day 22 may be performed at a local facility.
  Rationale: To ease patient travel burden to the clinical site.
- Some Cycle 1 Day 1 assessments made optional at the judgment of the investigator if these assessments from Screening occurred within 2 days of Cycle 1 Day 1.
  Rationale: To reduce number of required assessments on Cycle 1 Day 1.
- PET/CT clarified as an imaging modality.
  Rationale: To indicate that PET/CT is an acceptable imaging modality for the study.
- Gamma glutamyl transferase (GGT) added as part of serum chemistry assessment.
  Rationale: To include GGT as a safety assessment.

- Concomitant medication precautions added for patients on proton pump inhibitors and/or warfarin.
  Rationale: To include precautions due to potential drug-drug interactions.

Additional minor changes have been made to improve clarity and consistency.

ATTACHMENT 10: VERSION 6.0 SUMMARY OF CHANGES

- Sponsor name was changed.
  Rationale: To change the sponsor from Plexxikon to Daiichi Sankyo.
- Inclusion criteria 2 added to define KIT mutation.
  Rationale: To clarify the eligible study population with KIT mutation.
- Additional study assessment (whole blood sample collection) was added to the Schedule of Events for Phase II Portions.
  Rationale: To assess ctDNA in Phase 2 portion (only in Korea).
- Potential Risks and Benefits added.
  Rationale: To update potential risks and benefits based on safety data of other clinical studies.
- Additional criteria was added in DLT evaluation.
  Rationale: To clarify the DLT evaluation criteria for non-compliance (less than 80% of the planned dose).
- Recommended PLX3397 Dose Modifications was revised.
  Rationale: To update the Recommended PLX3397 Dose Modifications based on safety data of other clinical studies.
- Medical Monitor (Sponsor) was changed.
  Rationale: To change Medical Monitor based on the sponsor change.
- Hy's Law case was added to Event of special interest (Chapter 13) and emergency reporting.
  Rationale: To add the Hy's Law case for emergency reporting based on safety data of other clinical studies.
- Summary of Known KIT Mutations in Melanoma and Their Sensitivity to PLX3397 and Other Approved Drugs (Table) was updated.
  Rationale: To update based on latest information.
- An Adjudication Committee was added.
  Rationale: To assess hepatic safety and tolerability of the subjects, the judicationCommittee meetings will be held as needed.
- Finance and insurance (15.15) was added.
  Rationale: To clarify the sponsor's responsibility for finance and insurance.
- Address list was added in Attachment 5.
  Rationale: To clarify the contact person.

Additional minor changes have been made to improve clarity and consistency.

ATTACHMENT 11: VERSION 7.0 SUMMARY OF CHANGES

- Inclusion criteria 9, exclusion criteria 14 and 15 were revised.
  Rationale: To mitigate the risk of liver function abnormalities for patients enrolled in the study.
- Foot note was added into Schedule of Events for Pilot Portion of Study (Table 2-1) and Schedule of Events for Phase II Portion of Study (Table 2-2).
  Rationale: To reference the frequency of liver function test based on the revision of Recommended PLX3397 Dose Modifications for Liver Function Abnormalities (Table 7-2).
- Recommended PLX3397 Dose Modifications (Table 7-1) was revised and added Table 7-2 (Recommended PLX3397 Dose Modifications for Liver Function Abnormalities) and Table 7-3 (Additional Liver Evaluation).
  Rationale: To mitigate the risk to patients of increased aminotransferases with or without associated hyperbilirubinemia.
- The contact information for the Medical Monitor and safety reporting was changed.
  Rationale: To replace the Medical Monitor and safety reporting information.
- Address list was revised (ATTACHMENT 5)
  Rationale: To update or replace the medical monitor, CRO person, and Vender persons.

ATTACHMENT 12: VERSION 8.0 SUMMARY OF CHANGES

- Updated study information and design

  Rationale: the Sponsor decided to discontinue this study, and evaluate the study procedures. The Sponsor added an extension part in the study to allow subjects to continue receiving study drug, monitor for safety, and decrease the amount of procedures.