CLINICAL STUDY PROTOCOL

Protocol Number:	PLX121-01
Title:	A Phase 1b and 2a Study to Assess Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PLX9486 as a Single Agent and in Combination with PLX3397 or Sunitinib (Sutent®) in Patients with Advanced Solid Tumors and Patients with Locally Advanced, Unresectable, or Metastatic Gastrointestinal Stromal Tumor (GIST) Who Have Been Previously Treated with Imatinib Mesylate/KIT-Directed Tyrosine Kinase Inhibitor (TKI) Therapy
Indication:	Gastrointestinal Stromal Tumor (GIST)
Phase:	1b/2a
Sponsor:	Plexxikon Inc. 91 Bolivar Drive Berkeley, CA 94710, USA Telephone: [redacted]
IND Number:	123,295
Eudra CT Number:	Not applicable
Therapeutic Area:	Antineoplastic agent
Medical Monitor:	[redacted]
Protocol History:	
Date/Version	**23 July 2019/Amendment 7** **05 January 2018/Amendment 6** **08 February 2017/Amendment 5** **12 February 2016/Amendment 4** **05 June 2015/Amendment 3** **07 April 2015/Amendment 2** **12 February 2015/Amendment 1** **06 January 2015/Original**

Protocol PLX121-01: A Phase 1b and 2a Study to Assess Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PLX9486 as a Single Agent and in Combination with PLX3397 or Sunitinib (Sutent®) in Patients with Advanced Solid Tumors and Patients with Locally Advanced, Unresectable, or Metastatic Gastrointestinal Stromal Tumor (GIST) Who Have Been Previously Treated with Imatinib Mesylate/KIT-Directed Tyrosine Kinase Inhibitor (TKI) Therapy

1.0 SPONSOR SIGNATURE

I have read and approved this protocol.

Chief Medical Officer or Designee [redacted]	Date of Signature (DD Month YYYY)

2.0 INVESTIGATOR AGREEMENT AND SIGNATURE

I have read and approved this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Principal Investigator Signature	Date of Signature (DD Month YYYY)

Principal Investigator Name and Title (print)

Investigational site or name of institution and location (printed)

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3.0 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation or Term	Definition/Explanation
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	anaplastic thyroid carcinoma
ATP	adenosine triphosphate
AUC_{0-n}	area under the concentration-time curve from time zero to n hours after dosing
β-HCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CRPC	castration-resistant prostate cancer
C_{max}	maximum observed concentration
CRF	case report form
CTA	clinical trial agreement
CT	computed tomography
CTC	circulating tumor cell
DLT	dose-limiting toxicity
DoR	duration of response
DSMC	data and safety monitoring committee
ECG	electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
[redacted]	[redacted]
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
GIST	gastrointestinal stromal tumor
HED	human equivalent dose
ICH	International Conference on Harmonization
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
JM	Juxtamembrane
LDH	lactate dehydrogenase

Abbreviation or Term	Definition/Explanation
LFT	liver function test
LVEF	left ventricular ejection fraction
MEC	mucoepidermal carcinoma
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTcF	QT interval corrected using Fridericia equation
RBC	red blood cell
RP2D	recommended phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SDH	sorbitol dehydrogenase
STD_{10}	severely toxic dose in 10% of animals
SUSARs	suspected, unexpected serious adverse reactions
$T_{1/2}$	terminal elimination half-life
T_{max}	time to peak concentration
TDP	torsades de pointes
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
US	United States
USPI	US package insert
WBC	white blood cell
WHO	World Health Organization

4.0 PROTOCOL SYNOPSIS

Title:	A Phase 1b and 2a Study to Assess Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PLX9486 as a Single Agent and in Combination with PLX3397 or Sunitinib (Sutent®) in Patients with Advanced Solid Tumors and Patients with Locally Advanced, Unresectable, or Metastatic Gastrointestinal Stromal Tumor (GIST) Who Have Been Previously Treated with Imatinib Mesylate/KIT-Directed Tyrosine Kinase Inhibitor (TKI) Therapy
Sponsor:	Plexxikon Inc.
Clinical Phase:	1b/2a
Indication(s):	Gastrointestinal stromal tumor (GIST)
Objectives:	Dose-evaluation Cohorts (Part 1): Primary Objectives: • To evaluate safety and pharmacokinetics (PK) of orally administered PLX9486 as single and as multiple doses • To establish the maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) in patients with advanced solid tumors (including GIST) Secondary Objective: • To evaluate the efficacy of PLX9486 in solid tumors as measured by overall response rate (ORR) (by RECIST 1.1), duration of response (DoR), and progression-free survival (PFS). Exploratory Objective: • To assess biomarkers in peripheral blood, in archival tumor tissue, and in tumor biopsies Extension Cohorts (Part 2): Primary Objectives: [redacted] **Part 2b.** Assess the safety and tolerability of the combination of PLX9486 and PLX3397 and to establish an RP2D of PLX9486 in combination with PLX3397 in patients with advanced solid tumors (including GIST). [redacted] **Part 2e.** Assess the safety and tolerability of the combination of PLX9486 and sunitinib and to establish an RP2D of PLX9486 in combination with sunitinib in patients with advanced solid tumors (including GIST). [redacted]

	Secondary Objectives:
	• To determine the PK of PLX9486 as a single agent and in combination with PLX3397 or sunitinib.
	• [redacted]
	• To estimate the following:
	  • ORR (using RECIST 1.1)
	  • CBR (Parts 2b and e)
	  • OS (overall survival) and 12-month OS rate
	  • PFS and 6-month PFS rate
	  • Duration of response (DoR)
	Exploratory Objectives:
	• To assess biomarkers in peripheral blood and in archival tumor tissue
	• To assess tumor response in the Part 2 cohorts by Choi criteria (Choi 2007)

Study Design:	This Phase 1b and 2a, open-label, multicenter study includes a dose-evaluation portion (Part 1) in which the safety profile and RP2D of PLX9486 as a single oral agent administered daily in 28-day dosing cycles will be evaluated in patients with solid tumors (including GIST), followed by signal-seeking extension cohorts (Part 2) in which the following will be evaluated: [redacted] **Part 2b.** Open-label, sequential cohort dose-finding study of PLX9486 combined with PLX3397 in up to approximately 30 patients with solid tumors (including GIST) in a 3+3 design. [redacted]

	[redacted] **Part 2e.** Open-label, sequential cohort dose-finding study of PLX9486 combined with sunitinib in up to approximately 30 patients with solid tumors (including GIST) in a 3+3 design. [redacted] A review of the safety data from the 49 patients treated over the last 4 years suggested it was appropriate to reduce the frequency of surveillance. As of 26 April 2019 the clinical safety experience with PLX9486, either alone or in combination with PLX3397 or sunitinib, can be summarized as follows: • The most common AEs considered related to PLX9486 monotherapy, as well as PLX9486 in combination with PLX3397or sunitinib, were fatigue, diarrhea, and nausea. • A subject receiving PLX9486 1000 mg QD in Part 1 of Study PLX121 01 experienced the only DLT to date: a possibly related Grade 3 event of anemia. The subject's dose of PLX9486 was not changed and the event resolved. • One SAE of anemia considered possibly related to both PLX9486 and sunitinib was reported. No other treatment-related SAEs or deaths have been reported. Patients were enrolled in Parts 1, 2b, and e only and that as of the date of this protocol amendment patients are being treated in Parts 2b and e only.
Number of Patients:	**Part 1.** Enrollment in the single-agent dose escalation part is planned to be accrued using a standard"3+3" study design and will include up to approximately 30 solid tumor patients to evaluate PK and observed toxicity. Additional patients may be required, depending on the number of cohorts and evaluable patients needed. [redacted] **Part 2b.** Enrollment in the combination treatment part of the study (i.e., dose-finding for the PLX9486 and PLX3397 combination) is planned to be accrued using a standard "3+3" study design. Part 2b of the study is to include up to approximately 30 solid tumor patients (including GIST patients who have failed approved therapies and at the discretion of the investigator). Additional patients may be required depending on the need for additional cohorts or evaluable patients. [redacted] **Part 2e.** Enrollment in the combination treatment part of the study (i.e., dose-finding for the PLX9486 and sunitinib combination) is planned to be accrued using a standard "3+3" study design. Part 2e of the study is to include up to approximately 30 solid tumor patients (including GIST patients who have failed approved therapies and at the discretion of the investigator). Additional patients may be required depending on the need for additional cohorts or evaluable patients. [redacted]

Inclusion Criteria:	1. Male or female ≥18 years old 2. **Part 1, Part 2b, [redacted] and Part 2e**: Patients with advanced solid tumors who have tumor progression following standard therapy, have treatment-refractory disease, or for whom there is no effective standard of therapy 3. [redacted] 4. [redacted] 5. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at Screening (≤7 days prior to the first dose of study drug) and must agree to use an effective form of contraception from the time of the negative pregnancy test up to 6 months after the last dose of study drug. Effective forms of contraception include abstinence, hormonal contraceptive in conjunction with a barrier method, or a double-barrier method. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. WOCBP are defined as females who have experienced menarche, have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and are not postmenopausal. All females are considered to be WOCBP except if they have been postmenopausal or surgically sterile for ≥1 year. 6. Fertile men must agree to use an effective method of birth control during the study and for up to 6 months after the last dose of study drug. Male subjects with partners who are either pregnant or become pregnant during the study drug treatment period must agree to continue to use a condom for 90 days after the last dose of study drug. 7. All associated toxicity from previous or concurrent cancer therapy must be resolved (to ≤Grade 1 or Baseline) prior to study drug administration. 8. Willing and able to provide written informed consent prior to any study-related procedures and to comply with all study requirements. 9. ECOG Performance Status 0–2 10. Life expectancy ≥3 months 11. Adequate hematologic, hepatic, and renal function: a. absolute neutrophil count ≥1.5 × 10^9/L b. Hemoglobin >8 g/dL c. platelet count ≥100 × 10^9/L d. AST and ALT ≤upper limit of normal (ULN) e. Total bilirubin and direct bilirubin ≤ULN with an exception of patients with confirmed Gilbert's syndrome. For patients with confirmed Gilbert's syndrome, the total bilirubin should be ≤1.5 × ULN

	f. creatinine ≤1.5 × ULN or calculated CrCl >60 mL/min (using Cockcroft-Gault formula) g. PT (INR) ≤1.5 × ULN Note: Patients may be transfused prior to study entry. 12. Left ventricular ejection fraction (LVEF) >50% per echocardiogram or MUGA for patients on the sunitinib arms (Parts 2e and [redacted])
Exclusion Criteria	1. Known or demonstrated wild-type KIT or PDGF-R or known or demonstrated mutations of PDGF-R, SDH, or NF-1 that are causative for the observed malignancy 2. Part 1 (phase 1, single agent): Patients with a known or presumed pathogenic KIT exon 13 or 14 resistance mutation 3. [redacted] 4. Presence of symptomatic or uncontrolled brain or central nervous system metastases. Patients with stable, treated brain metastases are eligible for this trial. However, patients must not have required steroid treatment for their brain metastases within 30 days of Screening. 5. Known or suspected allergy to the investigational agent or any agent given in association with this trial 6. Clinically significant cardiac disease, defined by any of the following: a. Clinically significant cardiac arrhythmias, including bradyarrhythmias and/or the need for anti-arrhythmic therapy (excluding beta blockers or digoxin). (Patients with controlled atrial fibrillation are not excluded.) b. Congenital long QT syndrome or concomitant medications known to prolong the QT interval except those required for infections that carry a low risk of QTc prolongation. (See Attachment 4 for a list of drugs known to prolong the QT interval and that carry a risk of inducing torsades de pointes.) c. A Fridericia-corrected QT interval of ≥450 msec (for males) or ≥470 msec (for females) at Screening d. History of clinically significant cardiac disease or congestive heart failure >New York Heart Association (NYHA) Class II. Patients must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months. e. Uncontrolled hypertension, defined by a systolic blood pressure >150 mmHg or a diastolic blood pressure >100 mmHg that has been confirmed by two successive measurements despite optimal medical management. f. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within the 6 months before study drug initiation (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before study drug initiation) 7. Inability to take oral medication or significant nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate absorption 8. Ongoing infection of ≥Grade 2 severity 9. Non-healing wound, ulcer, or bone fracture

	10. Patient has known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection or is known to be a carrier of hepatitis B or C. Subjects who are positive for hepatitis C virus (HCV) antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible. Prior hepatitis infection that has been treated with highly effective therapy with no evidence of residual infection and with normal liver function (ALT, AST, total and direct bilirubin ≤ULN) is allowed. These patients must be willing to undergo additional testing per local standard of care. 11. Hepatobiliary diseases including biliary tract diseases, autoimmune hepatitis, inflammation, fibrosis, or cirrhosis of liver caused by viral, alcohol, or genetic reasons. Gilbert's disease is allowed if total bilirubin is ≤1.5 × ULN. 12. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent. 13. Females who are pregnant or nursing 14. Any psychological, familial, sociological, or geographical condition that could hamper compliance with the study protocol 15. Strong CYP3A4 inhibitors or inducers within 14 days or 5 drug half-lives of the agent, whichever is longer, of study drug initiation or the need to continue these drugs during this study. (A list of strong CYP3A4 inhibitors and inducers can be found in Attachment 2.) 16. Major surgery or significant traumatic injury within 14 days of Cycle 1 Day 1 17. History (within 2 years prior to first study drug administration) of another malignancy unless the malignancy was treated with curative intent and likelihood of relapse is small (<5% in 2 years in the judgment of the investigator). Subjects with a history of squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix may be enrolled. 18. Anti-cancer therapy within the period immediately before Cycle 1 Day 1: a. Chemotherapy, radiation therapy, small-molecule TKI therapy, or hormonal therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) of Cycle 1 Day 1. b. Immune therapy or other biologic therapy (other monoclonal antibodies or antibody-drug conjugates) for the treatment of cancer within 28 days of Cycle 1 Day 1.
Duration of Study:	Screening Period: 21 days (with the exception of tumor burden assessment [i.e., CT scan], which may be performed within 28 days of dosing. Treatment Period: **Part 1 and Part 2 (a–f).** Daily treatment with study drug for 28-day cycles until patient discontinuation or withdrawal or study termination. Follow-up Period: An end of study visit must occur ≥30 days after the last dose of PLX9486 and prior to starting any new anti-cancer therapy. 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.
Test Product, Dose, and Mode of Administration:	**Part 1 (Dose-escalation).** PLX9486 is formulated as a 50 mg tablet for oral use. Each treatment cycle will be 28 days. Cohorts of patients will be enrolled using the standard "3+3" design. The starting dose level of PLX9486 will be 250 mg/day (Cohort 1), using a once-daily (QD) dosing regimen, or for higher total daily doses, a split dosing schedule (e.g., twice-daily [BID]) may be studied at the current dose level under study or with previously studied daily dose levels. In the absence of Grade ≥2 toxicity that is considered "possibly" or "probably" related to the study agent and in conjunction with review of the PK data, dose escalation is planned to occur as indicated the following table:

Cohort Number	PLX9486 Dose Level (mg/day)[a]	Number and Unit Strength
[redacted]		
4	1000	20 × 50 mg
5	500 (BID)	10 × 50 mg (BID)
6	1500	30 × 50 mg
7	2000	40 × 50 mg

BID = twice daily

[a] Dosing interval/frequency will be QD unless otherwise specified (e.g., BID dosing).

Further dose escalation or de-escalation, and dosing schedules may be considered depending upon safety and PK findings and discussion between the Sponsor and the investigators. Dose escalation will continue unless there are dose-limiting toxicities (DLTs) in ≥2 of at least 6 patients (i.e., 33%) in one cohort within the first 28 days.

Also, dose escalation in smaller increments may be undertaken at any time based upon emerging safety, PK, and PD data.

If a DLT is observed in one patient in the initial cohort of 3 patients, an additional 3 patients will be treated at that dose. If DLT is observed in 2 or more patients of either 3 or 6 patients (i.e., ≥33% of patients treated) at a dose level, then a lower dose level of PLX9486 may be introduced unless no further reductions are feasible. If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, and convenience of dosing in approximately 3 to 6 patients treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days.

In addition, if the if the Study Committee determines that, in the absence of DLTs, enrollment of additional patients is required in order to better determine PK or safety, enrollment of an additional 3 patients may be undertaken at one or more of the dose levels already studied. Should more than 3 patients be accrued to a dose level for reasons other than DLT/toxicity, the decision to escalate further may be made after the first 3 patients clear the DLT window period after review of the available data by the Study Committee.

Once the safety and tolerability of a dose level have been established by all patients enrolled into the dose level cohort and treated for at least 28 days (one cycle), intra-patient dose escalation to that dose level will be permitted for patients at lower dose levels who have not experienced a Grade 3 or higher treatment-related toxicity that has not resolved to Grade ≤1. Additional PK samples may be requested for patients who dose escalate. In addition, additional PK samples may be requested for patients who experience a SAE, DLT, or AE of special interest.

[redacted]

Part 2b. Cohorts of patients will be enrolled using the standard "3+3" design. The PLX9486 dose escalation may follow the pattern established in Part 1, starting at ≤50% of the MTD/RP2D established in Part 1. In the absence of Grade ≥2 toxicity that is considered "possibly" or "probably" related to the study agent and in conjunction with review of the PK data, dose escalation in Part 2b is planned to occur as indicated in the following table:

Cohort Number	PLX9486 Dose Level (mg/day)[a]	PLX3397 (mg/day)
1	Approximately 50% of Part 1 RP2D	600 (200 mg in AM and 400 mg in PM)
2	Approximately 100% of Part 1 RP2D	600 (200 mg in AM and 400 mg in PM)
3	100% of Part 1 RP2D	400 mg QD (Cycles 1 and 2)
		600 mg QD (Cycle 3 +)[b]
4	TBD[c]	TBD[c]

RP2D = recommended Phase 2 dose

[a] PLX9486 administered once-daily (QD) or, for higher total daily doses, as split doses (e.g., twice-daily [BID]).

[b] At the discretion of the investigator and in the absence of clinically significant drug-related toxicity (Section 9.3) during Cycles 1 and 2.

[c] Based on a review of the data by the Study Committee.

Dose escalation will continue unless there are DLT in ≥2 of 6 patients in one cohort within the first 28 days of continuous dosing.

Further dose escalation and reduction in smaller increments may be undertaken at any time based upon emerging safety, PK, and PD data. Dose adjustments may also include increasing the number of patients at a given dose level as a result of the review of safety and PK data by the Sponsor and investigators. In addition, alternative dosing schedules may be explored, such as continuous dosing followed by a rest period, staggered dosing of the agents, etc., depending on the safety, PK, or PD-generated data, as well as data from other ongoing PLX3397 studies.

If a DLT is observed in one patient at a given cohort, an additional 3 patients will be enrolled into the cohort. If DLT is observed in ≥2 of at least 6 patients (i.e., ≥33%) at a dose level, then a lower dose level of PLX9486 may be introduced to the combination regimen. If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, and convenience of dosing in approximately 3 to 6 patients treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days.

Once the safety and tolerability of a dose level of PLX9486 in combination with PLX3397 have been established by 3 to 6 patients treated for 28 days (one cycle), intra-patient dose escalation to the next dose level may be permitted for patients at lower dose levels who have not experienced a Grade 3 or higher treatment-related toxicity that has not resolved.

[redacted]

[redacted]

Part 2e. Cohorts of patients will be enrolled using the standard "3+3" design. The PLX9486 dose escalation may follow the pattern established in Part 1, starting at 50% of the MTD/RP2D established in Part 1. In the absence of Grade ≥2 toxicity that is considered "possibly" or "probably" related to the study agent or dose-limiting toxicity (DLT) and in conjunction with review of the PK data, dose escalation in Part 2e is planned to occur as indicated in the following table:

Cohort Number	PLX9486 Dose Level (mg/day)[a]	Sunitinib Dose Level (mg/day)
1	Approximately 50% of Part 1 RP2D	25
2	100% of Part 1 RP2D	25
3	100% of Part 1 RP2D	37.5

BID = twice daily; RP2D = recommended Phase 2 dose

[a] Dosing interval/frequency will be QD unless otherwise specified (e.g., BID dosing).

Dose escalation will continue unless there are dose-limiting toxicities in ≥2 of 6 patients in one cohort within the first 28 days of continuous dosing.

Further dose escalation and reduction in smaller increments may be undertaken at any time based upon emerging safety, PK, and PD data. Dose adjustments may also include increasing the number of patients at a given dose level as a result of the review of safety and PK data by the Sponsor and investigators. In addition, alternative dosing schedules may be explored, such as continuous dosing followed by a rest period, staggered dosing of the agents, etc., depending on the safety, PK, or PD-generated data.

If a DLT is observed in one patient at a given cohort, an additional 3 patients will be enrolled into the cohort. If DLT is observed in ≥2 of at least 6 patients (i.e., ≥33%) at a dose level, then a lower dose level of PLX9486 may be introduced to the combination regimen. If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, and convenience of dosing in approximately 3 to 6 patients treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days.

Once the safety and tolerability of a dose level of PLX9486 in combination with sunitinib have been established by 3 to 6 patients treated for 28 days (one cycle), intra-patient dose escalation to the next dose level may be permitted for patients at lower dose levels who have not experienced a Grade 3 or higher treatment-related toxicity that has not resolved.

[redacted]

Definition of Dose-limiting Toxicity (DLT):	Dose-limiting toxicities (DLTs) are defined as AEs that occur during Cycle 1, are classified as possibly or probably related to the study drug, and meet one of the following CTCAE v4.03 criteria below.
	Hematologic Toxicities:
	• Grade 4 neutropenia lasting >7 days
	• Grade ≥3 neutropenia with fever
	• Grade 4 thrombocytopenia
	• Grade ≥3 thrombocytopenia lasting more than 7 days or associated with clinically significant bleeding
	• Grade 4 anemia
	Other Toxicities:
	• Any ≥Grade 3 (AE or laboratory) toxicity despite adequate supportive care/medical management except for the following:
	  • Grade ≥3 nausea, vomiting, or diarrhea that resolves to Grade ≤2 within 72 hours, with or without medical intervention or prophylaxis because this would not be considered treatment-limiting in an oncology population
	  • Grade 3 fatigue that resolves to ≤Grade 2 within 14 days because this would not be considered treatment-limiting in an oncology population
	  • Grade ≥3 asymptomatic changes in alkaline phosphatase, hypomagnesemia, hyperglycemia, or hypophosphatemia that are felt by the investigator to be clinically insignificant
	  • Grade 3 increases in transaminases confirmed upon repeat testing lasting ≤5 days
	• Any other Grade ≥3 toxicity (except those noted above) for which either the Principal Investigator or Sponsor deems further dose escalation inappropriate
	For **Part 1** and **Parts 2b** and **2e** in the absence of a DLT, patients must complete the first cycle of treatment (28 days) in order to be considered evaluable for DLT. Patients who discontinue for any reason other than a DLT or Grade ≥2 toxicity and have received less than 21 of 28 days of dosing will not be considered evaluable for DLT and will be replaced. This will be evaluated by the Study Committee.
	In the event of a fatal DLT that is possibly or probably attributed to study drug, further accrual to that dose level will be suspended pending review by the study committee. The Study Committee will review the available data regarding the event and provide recommendations.

Safety and Tolerability Assessments:	Safety and tolerability assessments will include physical examinations, vital signs, 12-lead electrocardiograms, AEs, hematology, complete chemistry panel, coagulation, and urinalysis.
Stopping Rules:	Dosing in a cohort will be stopped if ≥2 patients in any cohort of 6 patients (i.e., ≥33%) experience a DLT within the 28-day first cycle. Grade ≥3 treatment-related toxicities occurring beyond the first cycle will also be taken into consideration in determining discontinuation of dosing for a particular cohort. In addition, the Study Committee will evaluate/efficacy safety data on a periodic basis.
PK Parameters:	The PK profile of plasma PLX9486 will be analyzed by measurement of area under the plasma concentration-time curve [AUC_{0-9}. AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}], peak concentration (C_{max}), time to peak concentration (T_{max}), and half-life ($t_{1/2}$). The pharmacokinetic profile of plasma PLX3397 in Part 2b and [redacted] will be analyzed by measurement of area under the plasma concentration-time curve [AUC_{0-6}, AUC_{0-9}. AUC_{0-t}], peak concentration (C_{max}), and time to peak concentration (T_{max}).

	Dose proportionality following study medication will be explored by analyzing natural log-transformed pharmacokinetic variables, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate. Dose linearity for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} will also be explored by a linear model. The food effect of PLX9486 will be evaluated at a later time point. A potential interaction between the ADME profiles of PLX9486 and PLX3397 will be explored by determining the PK profiles of both drugs on the first and the last day of dosing in the first 28-day dosing cycle.
Pharmacodynamic Parameters:	Exploratory biomarkers for pharmacodynamics include, but are not limited to: • Genetic analyses of tumor tissues for mutations of KIT • Circulating tumor DNA in blood • Circulating tumor DNA and tumor biopsy-derived DNA (if available) will be analyzed for KIT exon mutations, PDGF-R, SDH, and NF-1 mutations to determine eligibility for the planned extension cohort. • Genomic analysis and expression arrays may also be performed for exploratory purposes.
Endpoints:	Part 1: The primary endpoints in Part 1 of the study include: • Establish the MTD/RP2D of single-agent PLX9486 in solid tumors • Safety endpoints (i.e., AEs, clinical laboratory evaluations, ECGs, physical examinations, and vital sign measurements) • Pharmacokinetic (PK) analysis The secondary endpoints in Part 1 of the study include: • ORR (RECIST 1.1) • PFS • DoR The exploratory endpoints of Part 1 of the study include: • Biomarkers/KIT mutational analysis in peripheral blood and in archival tumor tissue Part 2: [redacted] The primary endpoints for Parts 2b and 2e of the study include: • Establish the RP2D of PLX9486 in combination with PLX3397 or sunitinib • Safety and tolerability The secondary endpoints for Parts 2[redacted], of the study include: • ORR (RECIST 1.1) • CBR (Parts 2b, e) • PFS • OS • [redacted] • 12 month OS rate • 6 month PFS rate • Duration of response (DoR) The secondary endpoints for Parts 2[redacted] of the study include: • Pharmacokinetics (PK)

	The exploratory endpoints in Part 2[redacted] of the study include: • Biomarkers in peripheral blood and in archival tumor tissue • Tumor response in Part 2 cohorts by Choi criteria
Statistical Considerations	The sample sizes of the different parts of the study are based on clinical rather than statistical considerations. The dose-escalation cohorts (Part 1 and Parts 2b and 2e) follow a typical 3 + 3 design. Data will be tabulated and evaluated by descriptive statistics. [redacted]

Table 1: Trial Flow Chart – Part 1 (Single-agent PLX9486; 28-day Cycles)

STUDY DAY► / EVENT▼	SCR	Cycle 1						Cycle 2		Cycle 3+	Other	EOS[27]	FU[28]
	Day -21 to -1	Day 1	Day 2 + 1 d	Day 8 ±2 d	Day 15 ±2 d	Day 16 ±2 d	Day 22 ±2 d	Day 1 ±7 d	Day 15 ±3 d	Day 1 ±7 d			
Informed Consent	X												
Archival Tissue[1]	X												
Optional fresh tumor biopsy[2]	X												
Demographics and Medical History	X												
Prior Treatment for Primary Malignancy	X												
Height	X												
Weight	X	X		X	X		X	X	X	X		X	
Physical Exam[3]	X	X[4]		X	X		X	X	X	X		X	
Hematology[5]	X	X[4]		X	X		X	X	X	X		X	
Chemistry[6]	X	X[4]	X	X	X		X	X	X	X		X	
Coagulation Tests (PT/INR and PTT)	X	X[4]						X	X	X		X	
Tumor Markers[7]		X[4]						X	X	X		X	
Urinalysis[8]	X	X[9]		X	X		X	X	X	X		X	
12-Lead ECG[10]	X	X[11]			X[11]			X[11]		X[11]		X	
Vital Signs[12]	X	X[13]	X	X	X[13]	X	X	X	X	X		X	
Blood for PK[14, 15]		X	X		X	X	X	X	X	X		X	
Blood for PK (safety)[16]										X[16]			
Serum Pregnancy Test	X[17]											X	
ECOG Performance Status	X	X[4]		X	X		X	X	X	X		X	

Table 1: Trial Flow Chart – Part 1 (Single-agent PLX9486; 28-day Cycles), continued

STUDY DAY► / EVENT▼	SCR	Cycle 1						Cycle 2		Cycle 3+			
	Day -21 to -1	Day 1	Day 2 + 1 d	Day 8 ±2 d	Day 15 ±2 d	Day 16 ±2 d	Day 22 ±2 d	Day 1 ±7 d	Day 15 ±3 d	Day 1 ±7 d	Other	EOS[27]	FU[28]
Blood for Biomarker Assessment (PD)[15, 18]		X			X								
Circulating DNA[15, 19]	X	X			X			X	X	X		X	
PLX9486 Administration[20]		X[21]	X[21]	X[22]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	Daily[22]		
Radiographic Assessment of Tumor Burden (CT or MRI Scan)[23]	X									~Every 2 cycles	~Every 3 cycles after Cycle 12		
Compliance via Diary Review & Accountability				X	X		X	X[24]	X[24]	X[24]		X[24]	
Concomitant Medications[25]	X	X	X	X	X	X	X	X	X	X		X	
Adverse Events		X[26]	X[26]	X	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]		X	
Phone Interview													X

CBC = complete blood count; CXDX = Cycle number Day number; CT = computed tomography; ECG = electrocardiogram;
ECOG = Eastern Cooperative Oncology Group; EOS = end of study; INR = international normalized ratio; FU = follow-up; MRI = magnetic resonance imaging;
PD = pharmacodynamic; PK = pharmacokinetic; PT = partial thromboplastin; PTT = partial thromboplastin time;
QTcF = QT interval corrected for heart rate using Fridericia's method; SAE = serious adverse event; SCR = screening

1 Analysis for SDH, PDGF-R, and NF-1 mutations.
2 May be taken at any time from screening onward.
3 Complete physical exam at Screening and End of Treatment only. All other physical examinations may be abbreviated and symptom-directed.
4 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation tests, and tumor markers do not need to be repeated if these assessments from Screening occurred within 2 days of C1D1 **unless a change in status is suspected**.
5 Hematology evaluation must include CBC with differential and platelet count. Complete list of required tests are found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria.
6 Chemistry evaluation must include a complete metabolic panel including liver transaminases. Complete list of required tests are found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria.
7 To be performed as per institutional practice guidelines.

Table 1: Trial Flow Chart – Part 1 (Single-agent PLX9486; 28-day Cycles), continued

8 Urinalysis with urine dipstick is sufficient; if there is significant proteinuria, hematuria, or leukuria, a microscopic examination should be obtained. Complete list of required tests are found in Attachment 1 to the protocol.

9 Not required if Cycle 1 Day1 assessment is less than 7 days from Screening assessment.

10 Standard 12-lead ECG with QTcF calculation. Fridericia's correction is required. QTcF = (QT)/$\sqrt[3]{}$(RR). All ECGs should be obtained in triplicates (approximately 10 seconds for each ECG over a 5-minute period).

11 C1D1 ECGs will be obtained predose and at 3 hours postdose. C1D15 ECGs will be obtained predose and at 1, 3, 5, 7, and 9 hours postdose. Beginning at C2D1, ECG will be collected before dosing at the start of each cycle (e.g., C3D1, C4D1). All postdose ECGs should be collected at the specified time point ±30 minutes unless otherwise stated.

12 Predose vitals must be obtained on PK days. On non-PK, non-PD days, vital signs do not need to be predose and subjects may self-administer PLX9486 at home either prior to or after their clinic visit (if applicable).

13 Vitals to be obtained at 3 hours' postdose (±30 minutes).

14 Peripheral blood samples for the PK analysis of PLX9486 will be collected at:
Cycle 1 Day 1 at predose and 1, 3, 5, 7, and 9 hours postdose.
Cycle 1 Day 2 at predose only.
Cycle 1 Day 15 at predose and 1, 3, 5, 7, and 9 hours postdose.
Cycle 1 Day 16 at predose.
Cycle 1 Day 22 at predose.
Cycle 2 Day 1 at predose.
Cycle 2 Day 15 at predose.
Cycle 3+ Day 1 at predose.
One PK sample should be collected at the end of study visit for all subjects.
All Cycle 1 PK samples should be collected at the specified time points ±10 minutes at the 1 hour sample and ±30 minutes at subsequent time points.

15 Subjects must come into the clinic after an overnight fast of at least 8 hours. Subjects should remain fasting unless otherwise specified until after the dose of study drug is taken. Note: As of Amendment 6, subjects who were assigned to fast for at least 8 hours prior to dosing are no longer required to fast and may take their study medication with food.

16 Additional peripheral blood samples for PK may be requested for subjects who intrasubject dose escalate, who have an SAE, or have disease progression. For subjects who are able to intrasubject dose escalate to a higher dose level, PK to be obtained at predose and 1, 3, 5, 7, and 9 hours postdose on the first day of dose escalation and on Day 15 after dose escalation. A trough (predose) sample should be obtained on day 1 of subsequent cycles after dose escalation (i.e., if they intrasubject dose escalate at Cycle 2, collect the trough PK sample on Day 1 from Cycle 3 onwards). For subjects who experience a SAE or AE of special interest or a DLT, or have disease progression, a sample may be requested at the time of the event and the time of the last dose before the PK collection to be noted.

17 Serum pregnancy test must be negative within 7 days prior to C1D1 for women of child-bearing potential.

18 Peripheral blood samples for PD analysis will be obtained predose. The ±window does not apply to PD samples. PD samples must be obtained on the specified day whenever possible.

19 Whole blood for circulating DNA assessment to be obtained predose. Additional ctDNA samples may be requested for subjects upon disease progression.

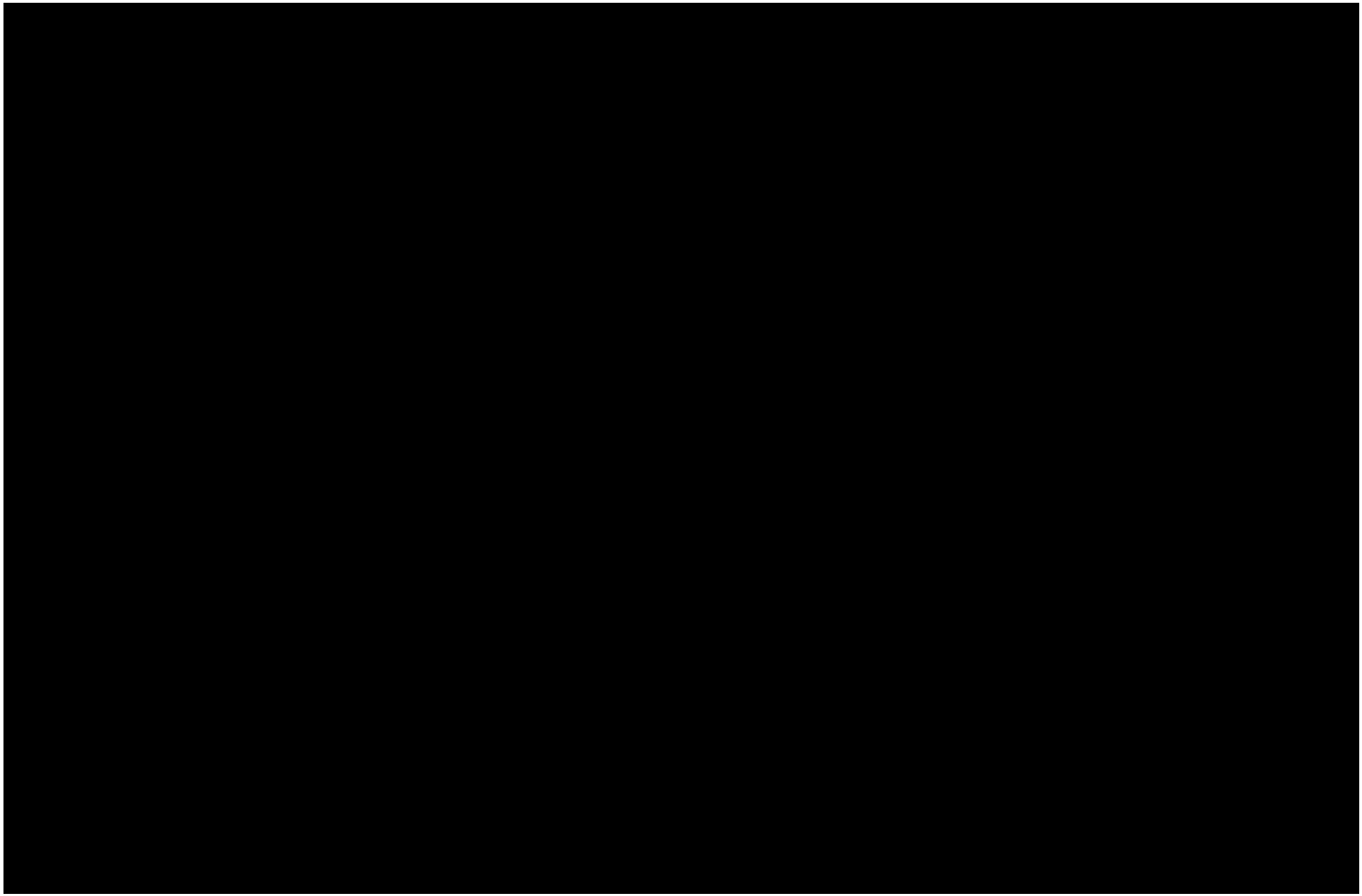
20 Subjects should fast approximately 1 hour before administration and approximately 2 hours after administration of PLX9486, unless otherwise specified.

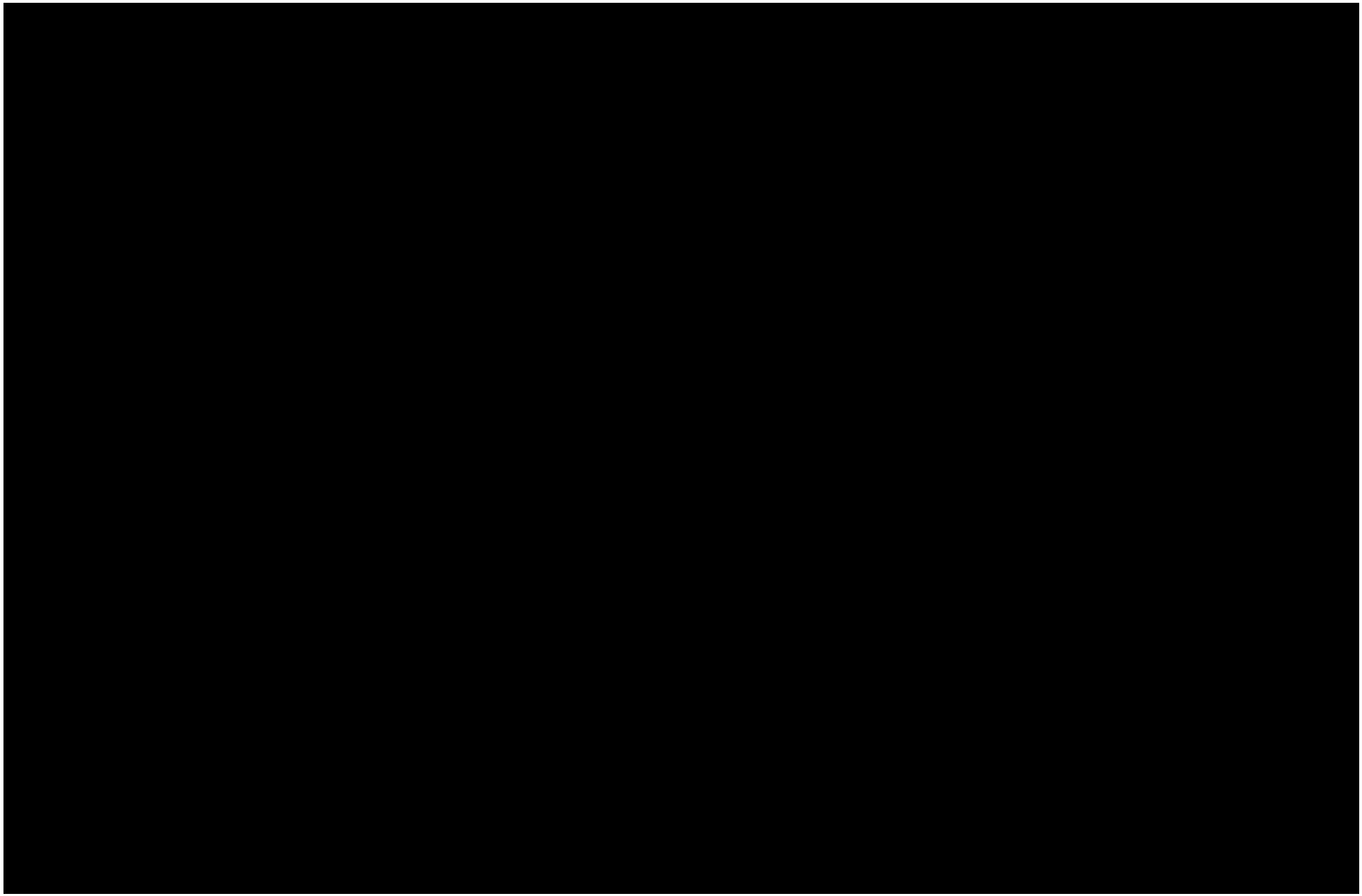
21 Subjects must receive their dose in the clinic. Subjects should be instructed not to take their PLX9486 dose at home on these visit days that include PK or PD collection. If alternate day dosing is used, subjects will be instructed on which days to take PLX9486 (e.g., even or odd numbered days).

Table 1: Trial Flow Chart – Part 1 (Single-agent PLX9486; 28-day Cycles), continued

22 Subjects may self-administer PLX9486 with water at home prior to or after their clinic visit on these days.
23 Screening radiographic assessment of tumor burden may be performed within 28 days of C1D1. After C1D1, radiographic assessment of tumor burden will be performed approximately every 2 cycles (e.g., after Cycle 2, 4, 6) or more frequently as clinically indicated. After Cycle 12, radiographic assessment of tumor burden may be performed every 3 cycles (e.g., after Cycle 15, 18, 21). Subjects obtaining PET CTs on study do not also need separate CT scans, and disease can be followed via PET CT. The Sponsor may request copies of the scans and reports for purposes of central review.
24 Drug diary to be reviewed and collected. Distribution of new drug diary.
25 Review of concomitant medications must include all medications taken within 28 days prior to Screening.
26 AE monitoring both predose and postdose on these days when PLX9486 is taken in the clinic.
27 This visit must occur ≥30 days **after** last dose of PLX9486 and prior to starting any new anti-cancer therapy.
28 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, response, and survival status.

Table 2: [redacted]





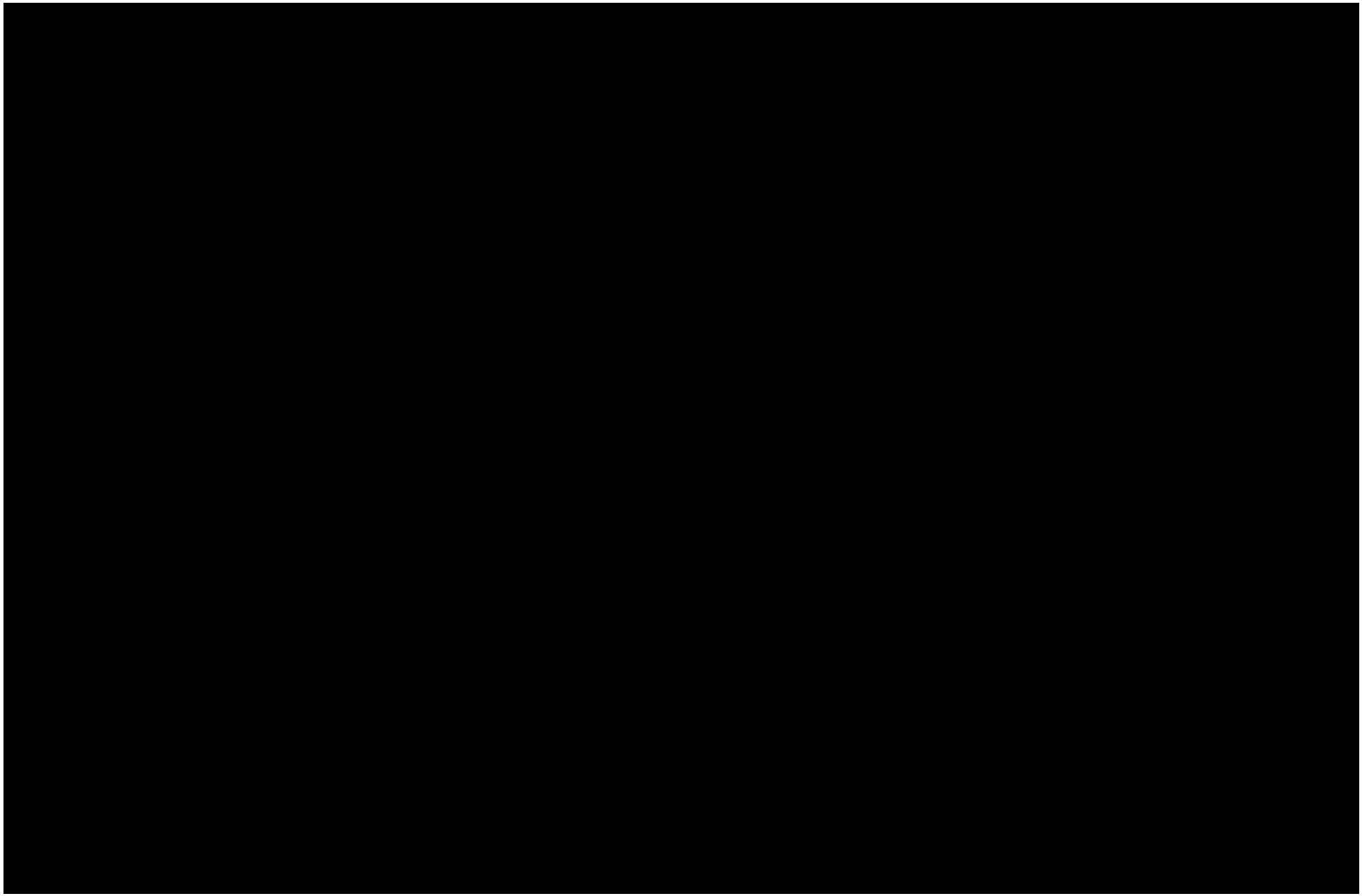


Table 3: Trial Flow Chart – Part 2b (Combination PLX3397 with PLX9486; 28-day Cycles)

STUDY DAY► / EVENT▼	SCR	Cycle 1						Cycle 2				Cycle 3+	Cycle 5+	EOS[27]	FU[28]
	Day -21 to -1	Day 1	Day 2 + 1d	Day 8 ±2 d	Day 15 ±2 d	Day 16 + 2 d	Day 22 + 2 d	Day 1 ±7 d	Day 8 ±2 d	Day 15 ±3 d	Day 22 ±2 d	Day 1 ±7 d	Day 1 ±7 d		
Informed Consent	X														
Archival Tissue[1]	X														
Optional Fresh Tumor Biopsy[2]	X														
Optional Paired Tumor Biopsy	X							X							
Demographics and Medical History	X														
Prior Treatment for Primary Malignancy	X														
Height	X														
Weight	X	X		X	X		X	X	X	X	X	X	X[29]	X	
Physical Exam[3]	X	X[4]		X	X		X	X	X	X	X	X	X	X	
Hematology[5]	X	X[4]		X	X		X	X	X	X	X	X	X	X	
Chemistry[6]	X	X[4]	X	X	X		X	X	X	X	X	X	X	X	
Coagulation Tests (PT/INR and PTT)	X	X[4]						X				X	X	X	
Tumor Markers[7]		X[4]						X				X	X	X	
Urinalysis[8]	X	X[9]						X				X	X	X	
12-Lead ECG[10]	X	X[11]			X[11]			X[11]				X[11]	X	X	
Vital Signs[12]	X	X[13]	X	X	X	X[13]	X	X	X	X	X	X	X	X	
Blood for PK Analysis[14, 15]		X	X		X	X	X	X		X		X		X	

Table 3: Trial Flow Chart – Part 2b (Combination PLX3397 with PLX9486; 28-day Cycles), continued

STUDY DAY► EVENT▼	SCR	Cycle 1						Cycle 2				Cycle 3+	Cycle 5+	EOS[27]	FU[28]
	Day -21 to -1	Day 1	Day 2 + 1d	Day 8 ±2 d	Day 15 ±2 d	Day 16 + 2 d	Day 22 + 2 d	Day 1 ±7 d	Day 8 ±2 d	Day 15 ±3 d	Day 22 ±2 d	Day 1 ±7 d	Day 1 ±7 d		
Blood for PK (safety or intrapatient dose escalation patients only)[16]												X[16]	X		
Serum Pregnancy Test	X[17]													X	
ECOG Performance Status[29]	X	X[4]		X	X		X	X	X	X	X	X	X	X	
Blood for Biomarker Assessment (PD)[15, 18]		X			X										
Circulating DNA[15, 19]	X	X			X			X		X		X		X	
PLX9486 and PLX3397 Administration[20]		X[21]	X[21]	X[22]	X[21]	X[21]	X[21]	X[21]	X[22]	X[21]	X[22]	X[21]	X[22]		
Radiographic Assessment of Tumor Burden (CT or MRI Scan)[23]	X											Every 2 cycles	Every 3 cycles		
Compliance via Diary Review & Accountability				X	X		X	X[24]	X	X	X	X[24]	X[24]	X[24]	
Concomitant Medications[25]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X[26]	X[26]	X	X[26]	X[26]	X[26]	X[26]	X	X[26]	X	X[26]	X	X	
Phone Interview															X

Table 3: Trial Flow Chart – Part 2b (Combination PLX3397 with PLX9486; 28-day Cycles), continued

CBC = complete blood count; CXDX = Cycle number Day number; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOS = end of study; INR = international normalized ratio; FU = follow-up; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PT = partial thromboplastin; PTT = partial thromboplastin time; QTcF = QT interval corrected for heart rate using Fridericia's method; SAE = serious adverse event; SCR = screening

1 Analysis for SDH, PDGF-R, and NF-1 mutations.

2 May be taken at any time from screening onward.

3 Complete physical exam at Screening and End of Treatment only. All other physical examinations may be abbreviated, symptom-directed and, starting on C5D1, may be completed every 8 weeks (+/- 7 days) or more frequently as clinically indicated.

4 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation tests, and tumor markers do not need to be repeated if these assessments from Screening occurred within 2 days of C1D1 **unless a change in status is suspected**.

5 Hematology evaluation must include CBC with differential and platelet count. Complete list of required tests are found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria. Starting on C5D1, may be completed every 8 weeks (+/- 7 days).

6 Chemistry evaluation must include a complete metabolic panel including liver transaminases. Complete list of required tests is found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria. Starting on C5D1, may be completed every 8 weeks (+/- 7 days).

7 To be performed as per institutional practice guidelines.

8 Urinalysis with urine dipstick is sufficient; if there is significant proteinuria, hematuria, or leukuria, a microscopic examination should be obtained. Complete list of required tests is found in Attachment 1 to the protocol. Starting on C5D1, may be completed every 8 weeks (+/- 7 days) or more frequently as clinically indicated.

9 Not required if Cycle 1 Day1 assessment is less than 7 days from Screening assessment.

10 Standard 12-lead ECG with QTcF calculation. Fridericia's correction is required. QTcF = $(QT)/\sqrt[3]{(RR)}$. All ECGs should be obtained in triplicates (approximately 10 seconds for each ECG over a 5-minute period). Starting on C5D1, a single ECG may be completed every 8 weeks (+/- 7 days) or more frequently as clinically indicated.

11 On C1D1, an ECG will be obtained prior to dosing and at postdose Hours 3 and 6 (±1 hr). On C1D15, an ECG will be obtained prior to dosing and at and at postdose Hours 1, 3, 5, 7, and 9. Beginning with Cycle 2, an ECG will be obtained prior to dosing on Day 1 of each cycle (e.g., C2D1, C3D1, C4D1). Unless otherwise stated, the window for all postdose ECG assessment time points is ±30 minutes.

12 Predose vitals must be obtained on PK days. On non-PK, non-PD days, vital signs do not need to be predose and patients may self-administer PLX9486 at home either prior to or after their clinic visit (if applicable). Starting on C5D1, may be completed every 8 weeks (+/- 7 days) or more frequently as clinically indicated.

13 Vitals to be obtained at 3 hours postdose (±30 minutes).

14 Peripheral blood samples for PK analysis of PLX9486 and PLX3397 will be collected at:

Cycle 1 Day 1 at predose and 1, 3, 5, 7, and 9 hours postdose.

Cycle 1 Day 2 at predose only.

Cycle 1 Day 15 at predose and 1, 3, 5, 7, and 9 hours postdose.

Cycle 1 Day 16 at predose.

Table 3: Trial Flow Chart – Part 2b (Combination PLX3397 with PLX9486; 28-day Cycles), continued

Cycle 1 Day 22 at predose.

Cycle 2 Day 1 at predose.

Cycle 2 Day 15 at predose.

Cycle 3+ Day 1 at predose.

One PK sample should be collected at the end of study visit for all patients.

All Cycle 1 PK samples should be collected at the specified time points ±10 minutes at the 1 hour sample and ±30 minutes at subsequent time points.

15 Patients must come into the clinic after an overnight fast of at least 8 hours. Patients should remain fasting unless otherwise specified until after the dose of study drug is taken. Note: As of Amendment 6, subjects who were assigned to fast for at least 8 hours prior to dosing are no longer required to fast and may take their study medication with food.

16 Additional PK samples may be requested for patients who intrapatient dose escalate, who have an SAE or AE of special interest, a DLT, or disease progression, or by Sponsor request. A sample may be requeted at the time of the event and/or at the time of the last dose. For patients who are able to intrapatient dose escalate to a higher dose level, PK to be obtained at predose and 1, 3, 5, 7, and 9 hours postdose on the first day of dose escalation and on Day 15 after dose escalation.

17 Serum pregnancy test must be negative within 7 days prior to C1D1 for women of child-bearing potential.

18 Peripheral blood samples for PD analysis will be obtained predose. The ±window does not apply to PD samples. PD samples must be obtained on the specified day whenever possible.

19 Whole blood for circulating DNA assessment to be obtained predose. Additional ctDNA samples may be requested for patients upon disease progression.

20 Patients should fast approximately1 hour before administration and approximately 2 hours after administration of PLX9486, unless otherwise specified.

21 Patients must receive their dose in the clinic. Patients should be instructed not to take their PLX9486 dose at home on these visit days that include PK or PD collection. If alternate day dosing is used, patients will be instructed on which days to take PLX9486 (e.g., even or odd numbered days).

22 Patients may self-administer PLX9486 with water at home prior to or after their clinic visit on these days.

23 Screening radiographic assessment of tumor burden may be within 28 days of scheduled C1D1. After C1D1, radiographic assessment of tumor burden will be performed approximately every 2 cycles (e.g., after Cycle 2, 4, 6) or more frequently as clinically indicated. After C5D1, radiographic assessment of tumor burden may be performed every 3 cycles (e.g., after Cycle 8, 11, 14) or more frequently as clinically indicated. Patients obtaining PET CTs on study do not also need separate CT scans, and disease can be followed via PET CT. The Sponsor may request copies of the scans and reports.

24 Drug diary to be reviewed and collected. Distribution of new drug diary. May be collected every 8 weeks (+/- 7 days) from C5D1 on.

25 Review of concomitant medications must include all medications taken within 28 days prior to Screening.

26 AE monitoring both predose and postdose on these days when PLX9486 is taken in the clinic.

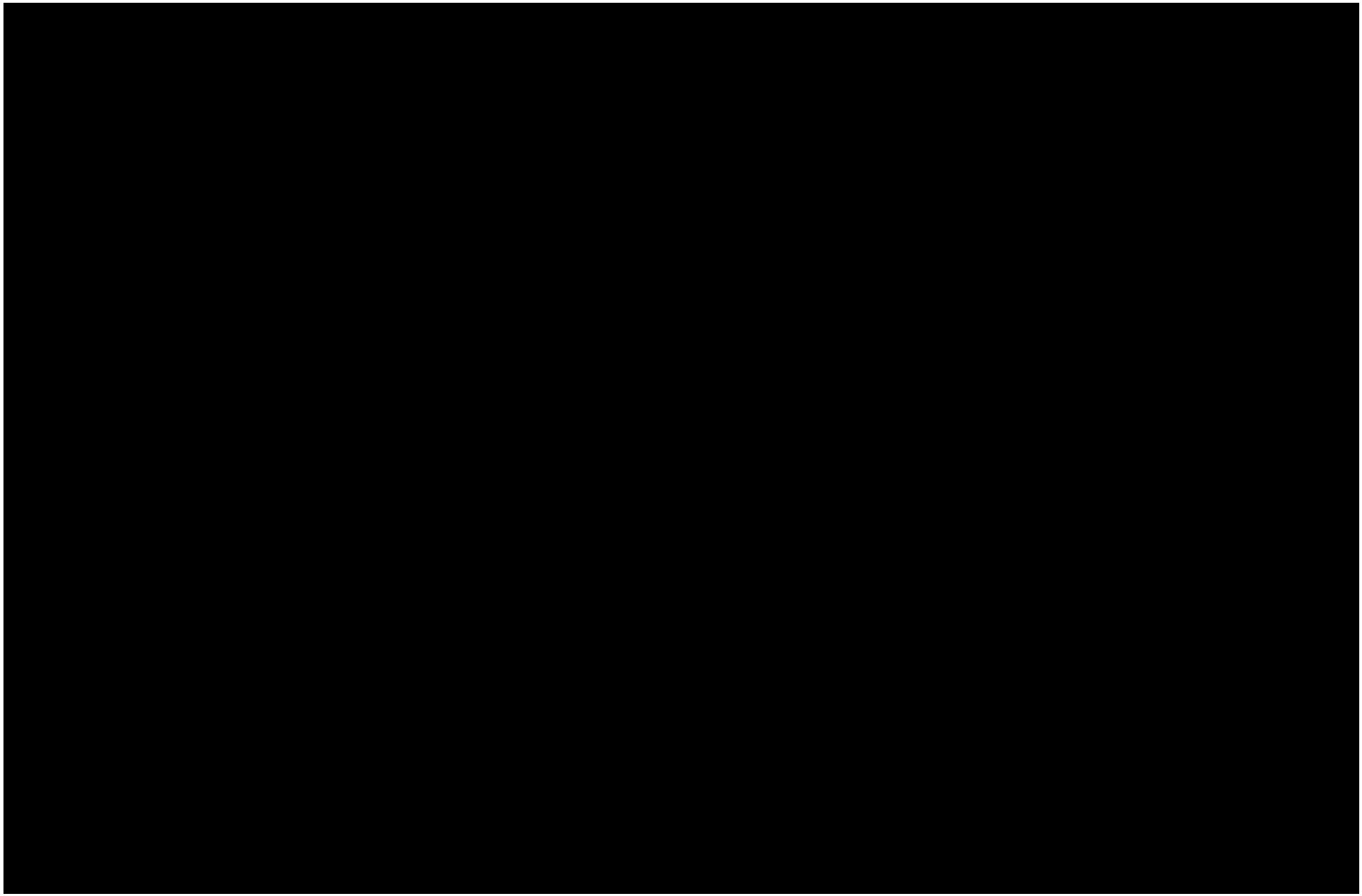
27 This visit must occur ≥30 days **after** last dose of PLX9486 and prior to starting any new anti-cancer therapy.

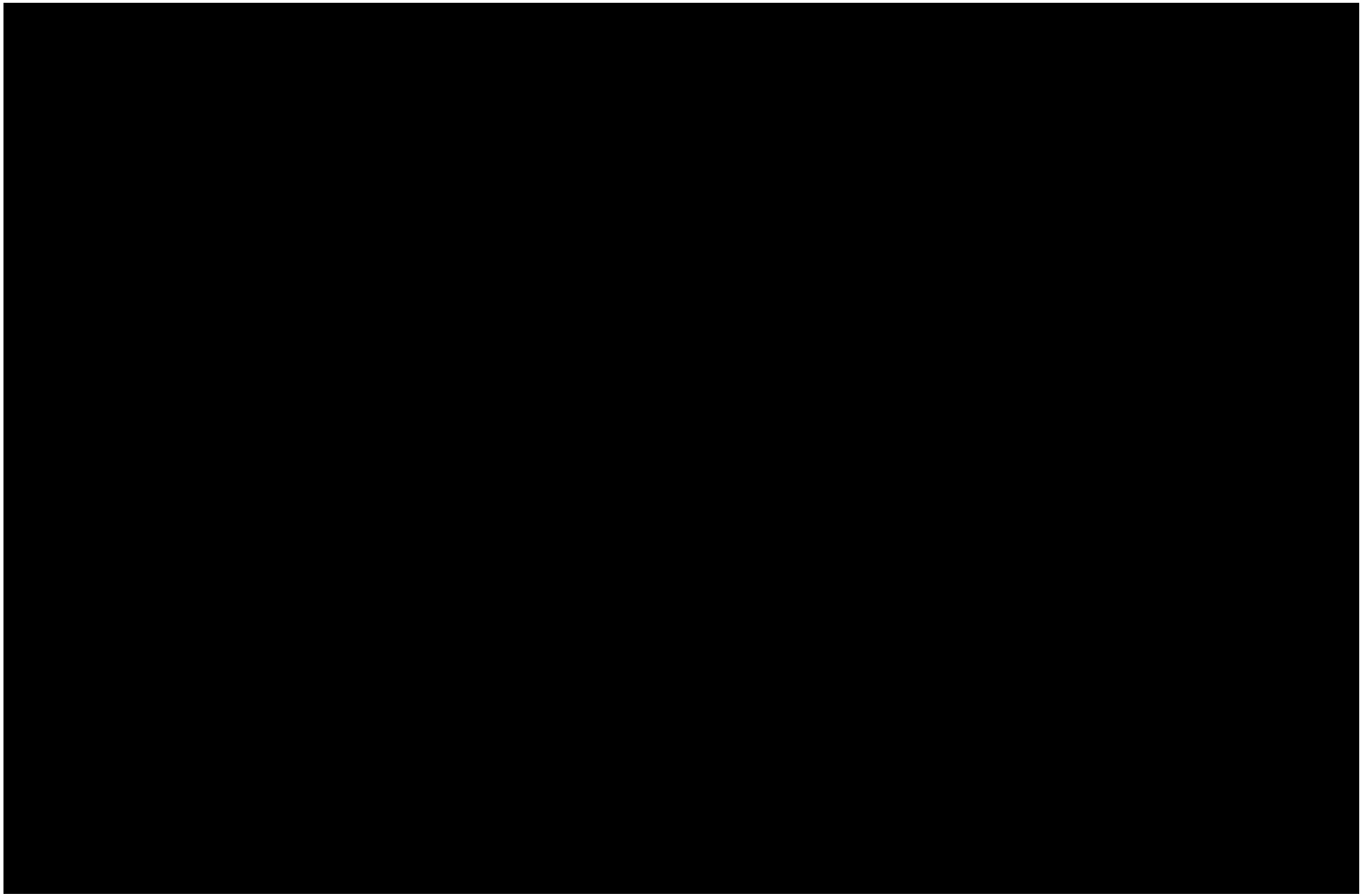
28 A post-study follow-up contact by phone by site staff will be conducted every 3 months during Year 1, then every 6 months thereafter to obtain information on any new anti-cancer therapy received, response, and survival status.

29 May be performed every 8 weeks (+/- 7 days) from C5D1 or more frequently as clinically indicated.

Table 4: [redacted]

[redacted]





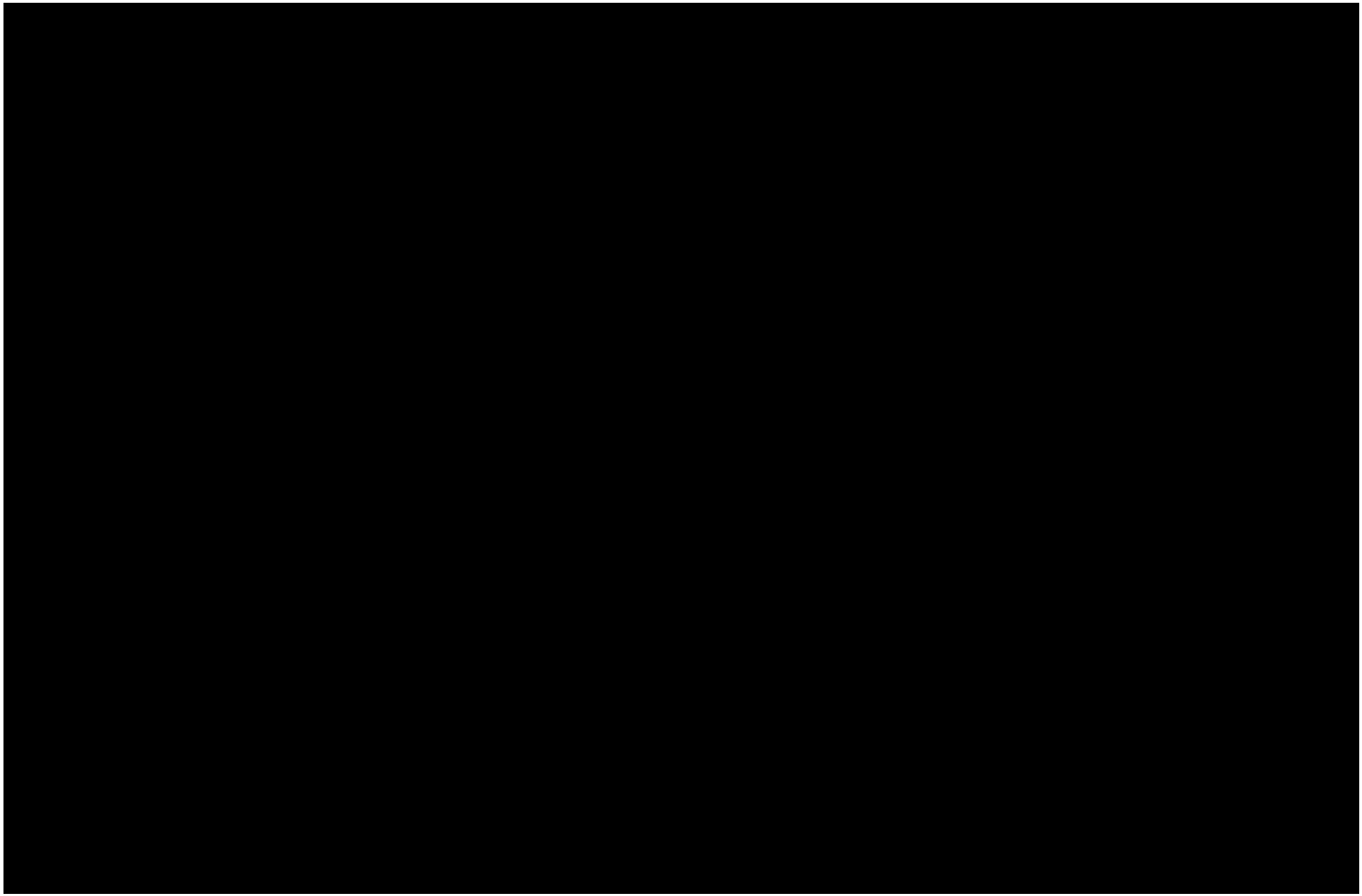
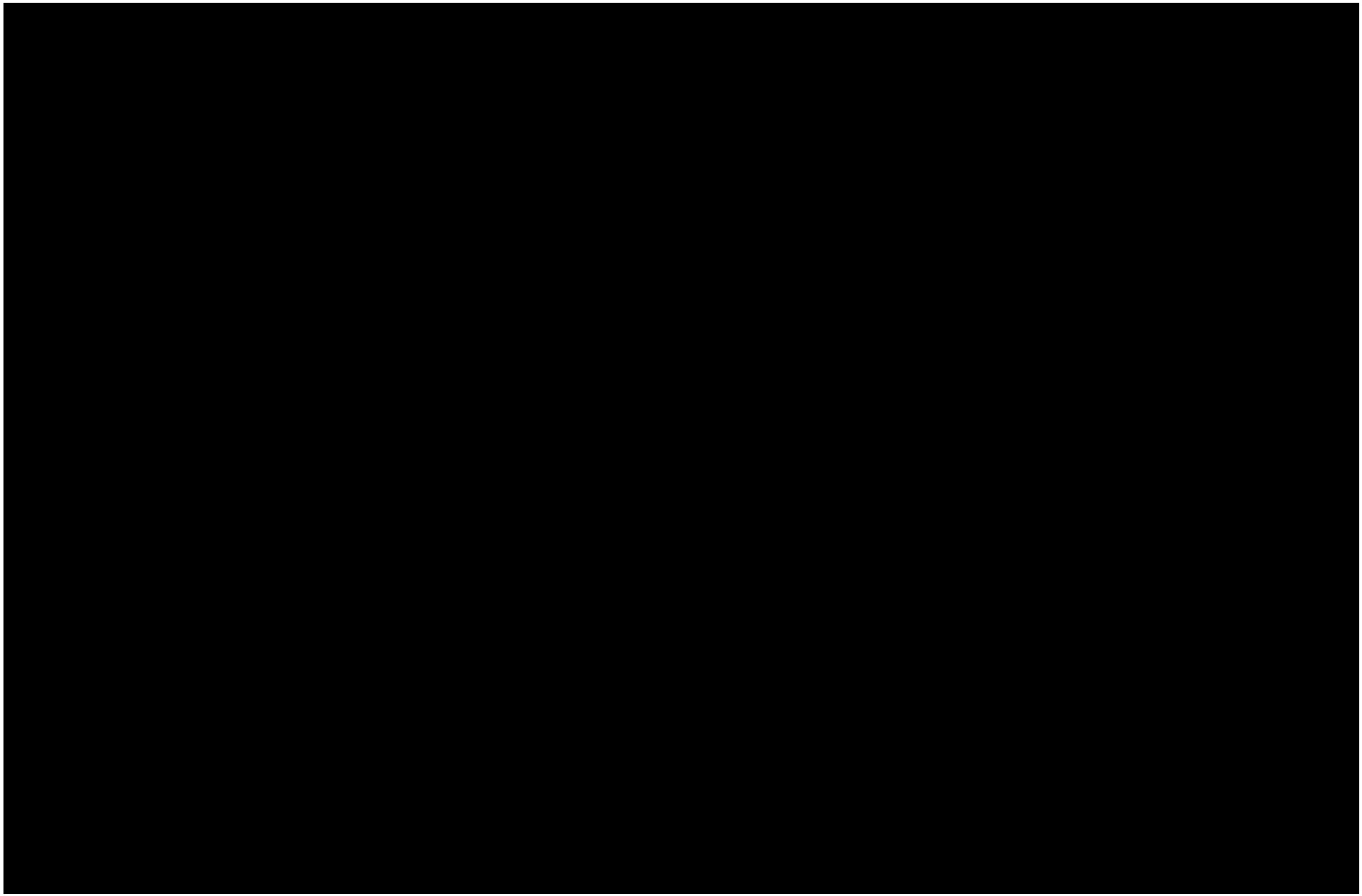
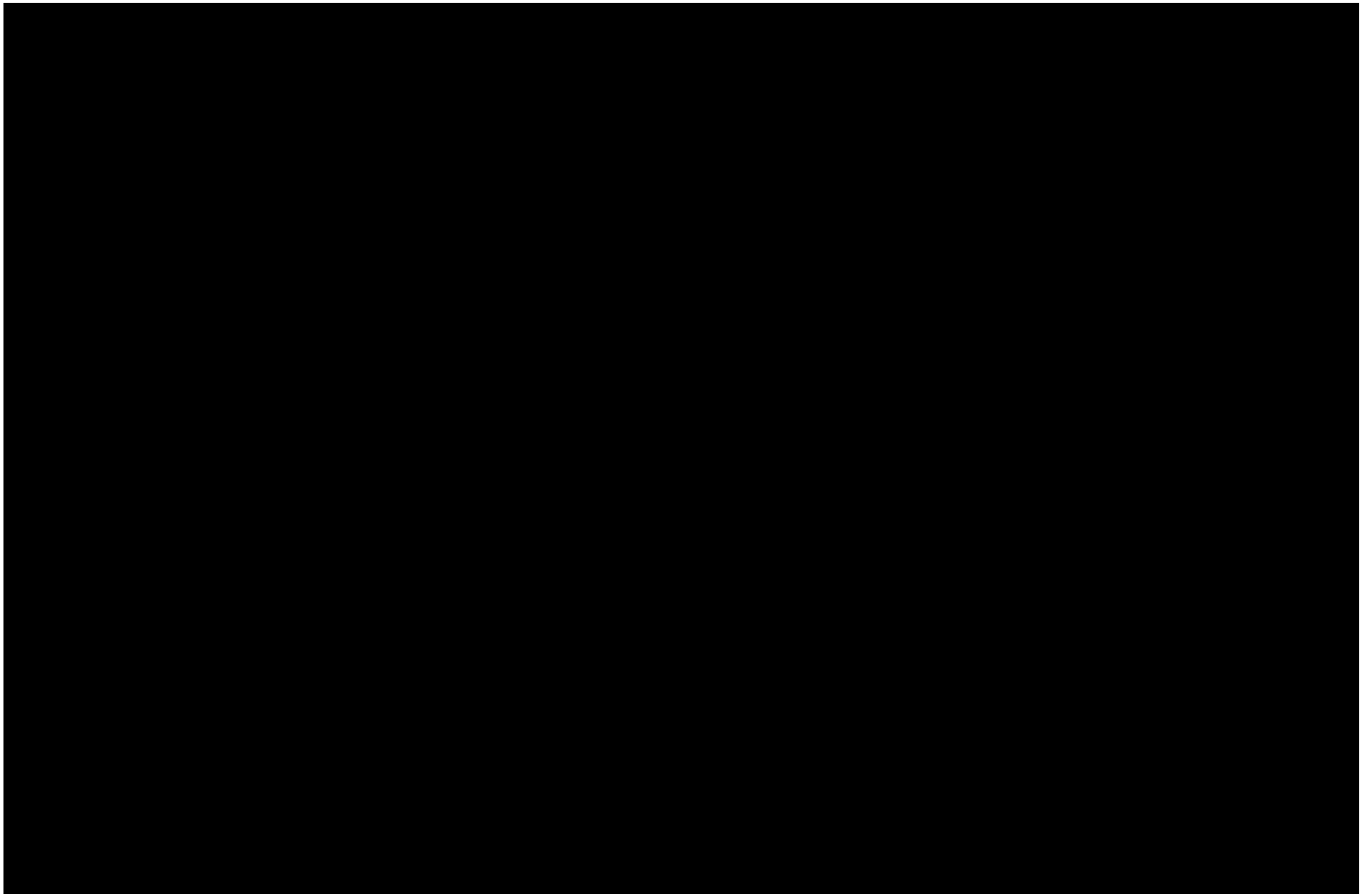


Table 5: [redacted]

[redacted]





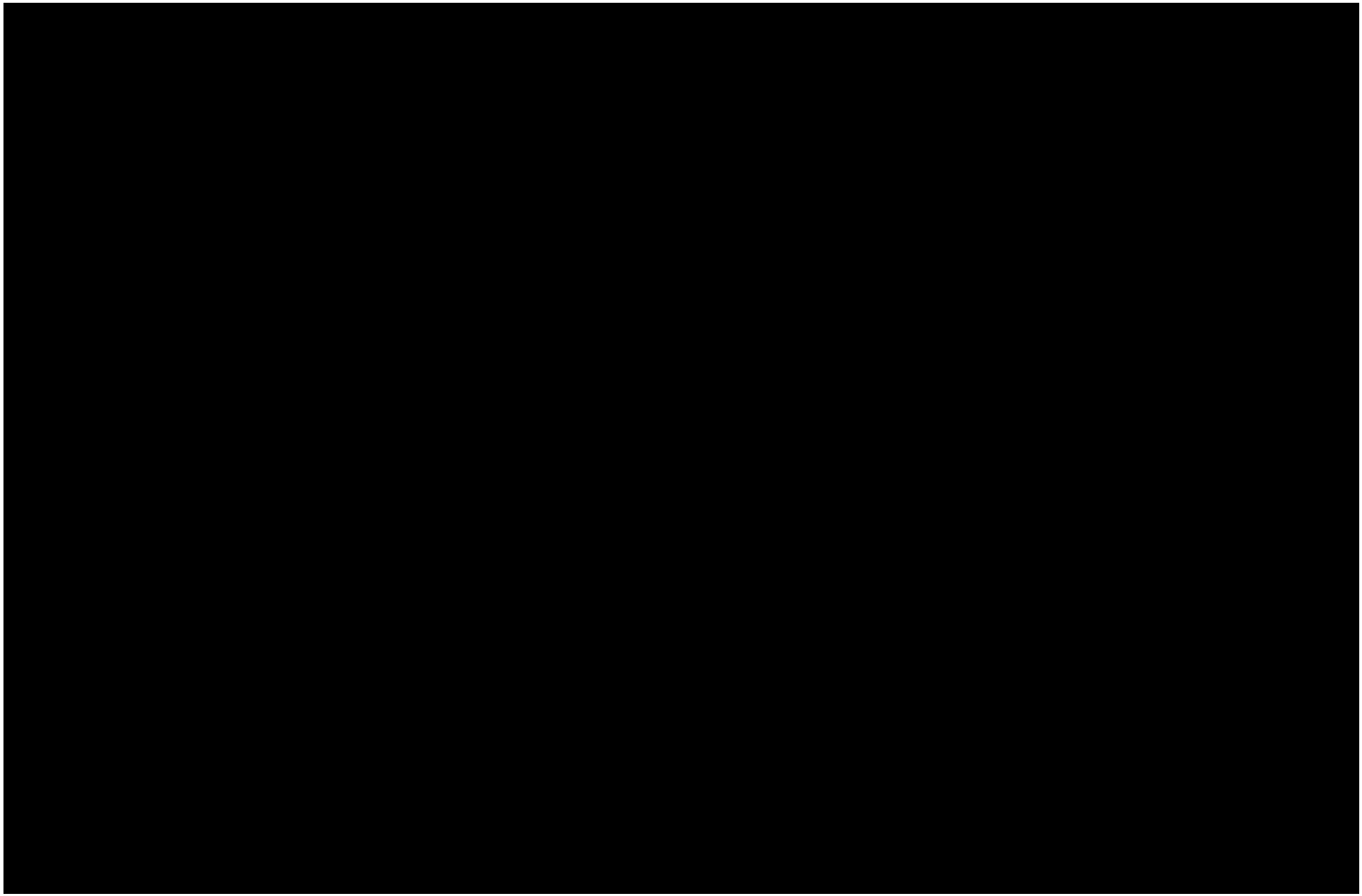


Table 6: Trial Flow Chart – Part 2e (Combination Sunitinib and PLX9486; 28-day Cycles)

STUDY DAY► / EVENT▼	SCR	Cycle 1						Cycle 2				Cycle 3+	Cycle 5+	EOS[27]	FU[28]
	Day -21 to -1	Day 1	Day 2 + 1 d	Day 8 ±2 d	Day 15 ±2 d	Day 16 + 2 d	Day 22 + 2 d	Day 1 ±7 d	Day 8 ±2 d	Day 15 ±3 d	Day 22 ±2 d	Day 1 ±7 d	Day 1 ±7 d		
Informed Consent	X														
Archival Tissue[1]	X														
Optional Fresh Tumor Biopsy[2]	X														
Optional Paired Tumor Biopsy	X							X							
Demographics and Medical History	X														
Prior Treatment for Primary Malignancy	X														
Height	X														
Weight	X	X		X	X		X	X	X	X	X	X	X[3]	X	
Physical Exam[3]	X	X[4]		X	X		X	X	X	X	X	X	X	X	
Hematology[5]	X	X[4]		X	X		X	X	X	X	X	X	X	X	
Chemistry[6]	X	X[4]	X	X	X		X	X	X	X	X	X	X	X	
Coagulation Tests (PT/INR and PTT)[30]	X	X[4]						X				X	X	X	
Tumor Markers[7]		X[4]						X				X	X	X	
Urinalysis[8]	X	X[9]						X				X	X	X	
12-Lead ECG[10]	X	X[11]			X[11]			X[11]				X[11]	X	X	
Vital Signs[12]	X	X[13]	X	X	X[13]	X	X	X	X	X	X	X	X	X	
MUGA or ECHO[29]	X											X	X		
TSH[29]	X											X	X		
Blood for PK[14, 15]		X	X		X	X	X	X		X		X		X	
Blood for PK (safety)[16]												X[16]	X		

Table 6: Trial Flow Chart – Part 2e (Combination Sunitinib and PLX9486; 28-day Cycles), continued

STUDY DAY► EVENT▼	SCR	Cycle 1						Cycle 2				Cycle 3+	Cycle 5+	EOS[27]	FU[28]
	Day -21 to -1	Day 1	Day 2 + 1 d	Day 8 ±2 d	Day 15 ±2 d	Day 16 + 2 d	Day 22 + 2 d	Day 1 ±7 d	Day 8 ±2 d	Day 15 ±3 d	Day 22 ±2 d	Day 1 ±7 d	Day 1 ±7 d		
Serum Pregnancy Test	X[17]													X	
ECOG Performance Status	X	X[4]		X	X		X	X	X	X	X	X	X[30]	X	
Blood for Biomarker Assessment (PD)[15, 18]		X			X										
Circulating DNA[15, 19]	X	X			X			X		X		X		X	
PLX9486 & Sunitinib Administration [20]		X[21]	X[21]	X[22]	X[21]	X[21]	X[21]	X[21]	X[22]	X[21]	X[22]	X[21]	X[22]		
Radiographic Assessment of Tumor Burden (CT or MRI Scan)[23]	X											Every 2 cycles	Every 3 cycles		
Compliance via Diary Review & Accountability				X	X		X	X[24]	X[24]	X	X[24]	X[24]	X[24]	X[24]	
Concomitant Medications[25]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X[26]	X[26]	X	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]	X	X	
Phone Interview															X

CBC = complete blood count; CXDX = Cycle number Day number; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; INR = international normalized ratio; FU = follow-up; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PT = partial thromboplastin; PTT = partial thromboplastin time; QTcF = QT interval corrected for heart rate using Fridericia's method; SAE = serious adverse event; SCR = screening; TSH = thyroid stimulating hormone

1 Analysis for SDH, PDGF-R, and NF-1 mutations.

Table 6: Trial Flow Chart – Part 2e (Combination Sunitinib and PLX9486; 28-day Cycles), continued

2 May be taken at any time from screening onward.

3 Complete physical exam at Screening and End of Treatment only. All other physical examinations may be abbreviated, symptom-directed and, starting on C5D1, may be completed every 12 weeks (+/- 7 days) or more frequently as clinically indicated (including weight).

4 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation tests, and tumor markers do not need to be repeated if these assessments from Screening occurred within 2 days of C1D1 **unless a change in status is suspected**.

5 Hematology evaluation must include CBC with differential and platelet count. Complete list of required tests are found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria. Starting on C5D1, may be completed every 12 weeks (+/- 7 days).

6 Chemistry evaluation must include a complete metabolic panel including liver transaminases. Complete list of required tests are found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria. Starting on C5D1, may be completed every 12 weeks (+/- 7 days) with LDH and uric acid as optional.

7 To be performed as per institutional practice guidelines.

8 Urinalysis with urine dipstick is sufficient; if there is significant proteinuria, hematuria, or leukuria, a microscopic examination should be obtained. Complete list of required tests are found in Attachment 1 to the protocol. Starting on C5D1, may be completed every 12 weeks (+/- 7 days) or more frequently as clinically indicated.

9 Not required if Cycle 1 Day1 assessment is less than 7 days from Screening assessment.

10 Standard 12-lead ECG with QTcF calculation. Fridericia's correction is required. QTcF = $(QT)/\sqrt[3]{(RR)}$. All ECGs should be obtained in triplicates (approximately 10 seconds for each ECG over a 5-minute period). Starting on C5D1, a single ECG may be completed every 12 weeks (+/- 7 days) or more frequently as clinically indicated.

11 On C1D1, an ECG will be obtained prior to dosing and at postdose Hours 3 and 6 (±1 hr). On C1D15, an ECG will be obtained prior to dosing and at postdose Hours 1, 3, 5, 7, and 9. Beginning with Cycle 2, an ECG will be obtained prior to dosing on Day 1 of every cycle (e.g., C2D1, C3D1). Unless otherwise stated, the window for all postdose ECG assessment time points is ±30 minutes.

12 Predose vitals must be obtained on PK days. On non-PK, non-PD days, vital signs do not need to be predose and patients may self-administer PLX9486 at home either prior to or after their clinic visit (if applicable). Starting on C5D1, may be completed every 12 weeks (+/- 7 days) or more frequently as clinically indicated.

13 Vitals to be obtained at 3 hours postdose (±30 minutes).

14 Peripheral blood samples for PK analysis of PLX9486 and sunitinib should be obtained at:

Cycle 1 Day 1 at predose and 1, 3, 5, 7, and 9 hours postdose.

Cycle 1 Day 2 at predose only.

Cycle 1 Day 15 at predose and 1, 3, 5, 7, and 9 hours postdose.

Cycle 1 Day 16 at predose.

Cycle 1 Day 22 at predose.

Cycle 3+ Day 1 should be obtained at predose.

One PK sample should be collected at the end of study visit for all patients.

Table 6: Trial Flow Chart – Part 2e (Combination Sunitinib and PLX9486; 28-day Cycles), continued

All Cycle 1 PK samples should be collected at the specified time points ±10 minutes at the 1 hour sample and ±30 minutes at subsequent time points.

15 Patients must come into the clinic after an overnight fast of at least 8 hours. Patients should remain fasting unless otherwise specified until after the dose of study drug is taken. Note: As of Amendment 6, patients who were assigned to fast for at least 8 hours prior to dosing are no longer required to fast and may take their study medication with food.

16 Additional PK samples may be requested for patients who intrapatient dose escalate, who have an SAE or AE of special interest, a DLT, have disease progression or by Sponsor request. A sample may be requested at the time of the event and/or at the time of the last dose. For patients who are able to intrapatient dose escalate to a higher dose level, PK to be obtained at predose and 1, 3, 5, 7, and 9 hours postdose on the first day of dose escalation and on Day 15 after dose escalation.

17 Serum pregnancy test must be negative within 7 days prior to C1D1 for women of child-bearing potential.

18 Peripheral blood samples for PD will be obtained predose. The ±window does not apply to PD samples. PD samples must be obtained on the specified day whenever possible.

19 Whole blood for circulating DNA assessment to be obtained predose. Additional ctDNA samples may be requested for patients upon disease progression.

20 Patients should fast approximately 1 hour before administration and approximately 2 hours after administration of PLX9486, unless otherwise specified.

21 Patients must receive their dose in the clinic. Patients should be instructed not to take their PLX9486 dose at home on these visit days that include PK or PD collection. If alternate day dosing is used, patients will be instructed on which days to take PLX9486 (e.g., even or odd numbered days).

22 Patients may self-administer PLX9486 with water at home prior to or after their clinic visit on these days.

23 Screening radiographic assessment of tumor burden may be within 28 days of scheduled C1D1. After C1D1, radiographic assessment of tumor burden will occur approximately every 2 cycles (e.g., after Cycle 2, 4, 6) or more frequently as clinically indicated. After C5D1, radiographic assessment of tumor burden may be performed every 3 cycles (e.g., after Cycle 8, 11, 14) or more frequently as clinically indicated. Patients obtaining PET CTs on study do not also need separate CT scans, and disease can be followed via PET CT. The Sponsor may request copies of the scans and reports.

24 Drug diary to be reviewed and collected. Distribution of new drug diary. May be collected every 24 weeks (+/- 7 days) from C5D1 on.

25 Review of concomitant medications must include all medications taken within 28 days prior to Screening.

26 AE monitoring both predose and postdose on these days when PLX9486 is taken in the clinic.

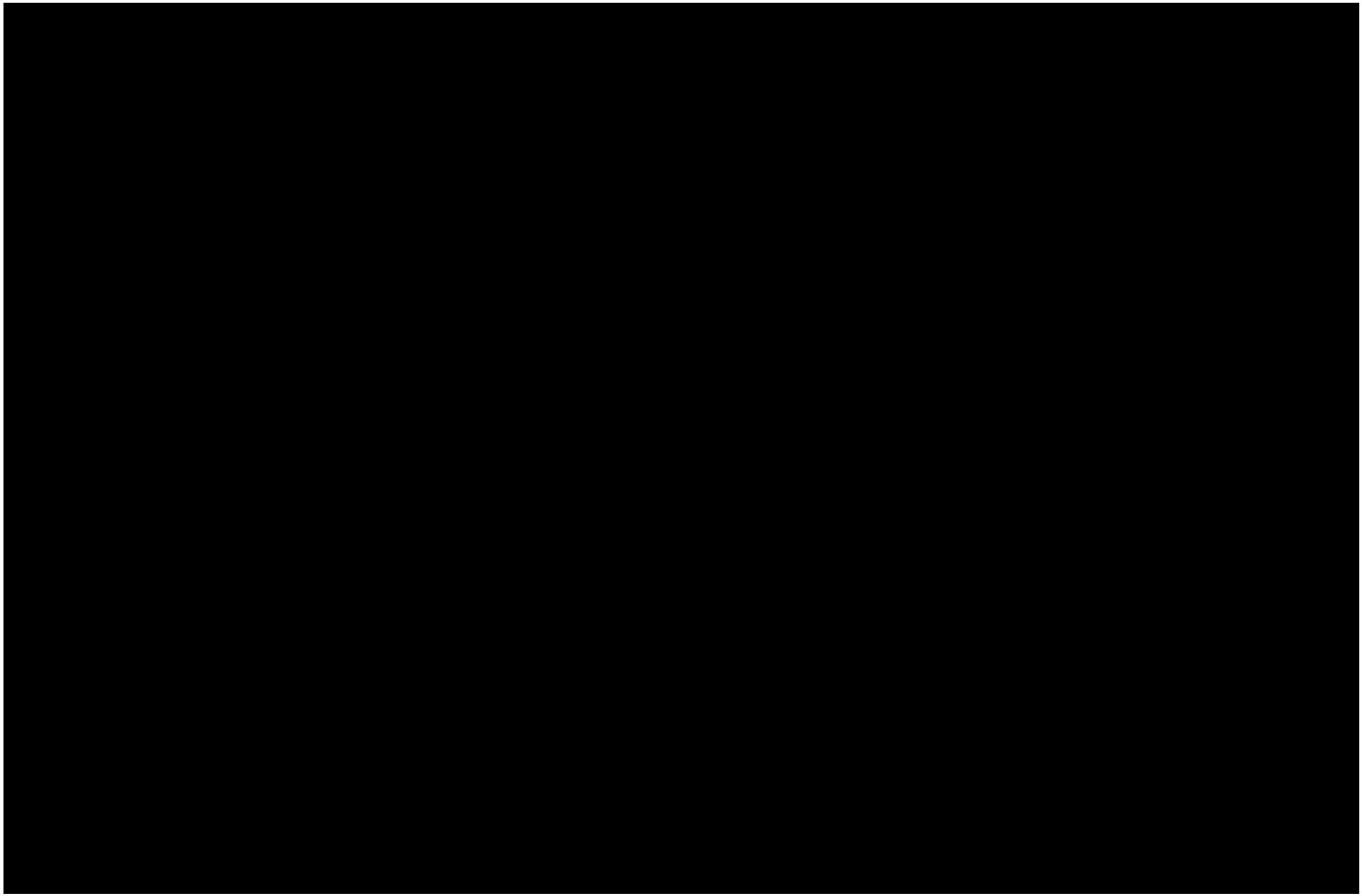
27 This visit must occur ≥30 days **after** last dose of PLX9486 and prior to starting any new anti-cancer therapy.

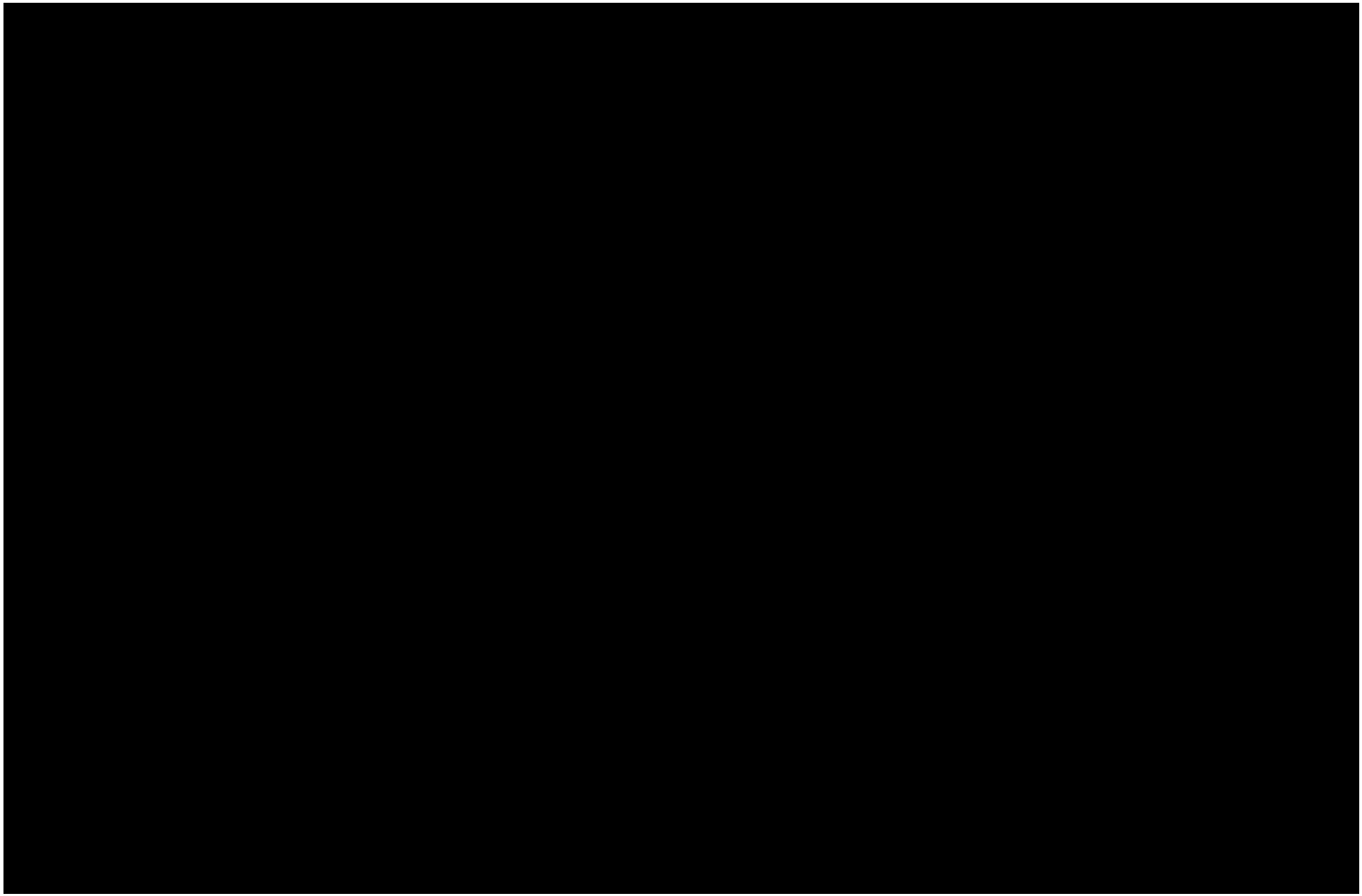
28 A post-study follow-up contact by phone by site staff will be conducted every 3 months during Year 1, then every 6 months thereafter to obtain information on any new anti-cancer therapy received, response, and survival status.

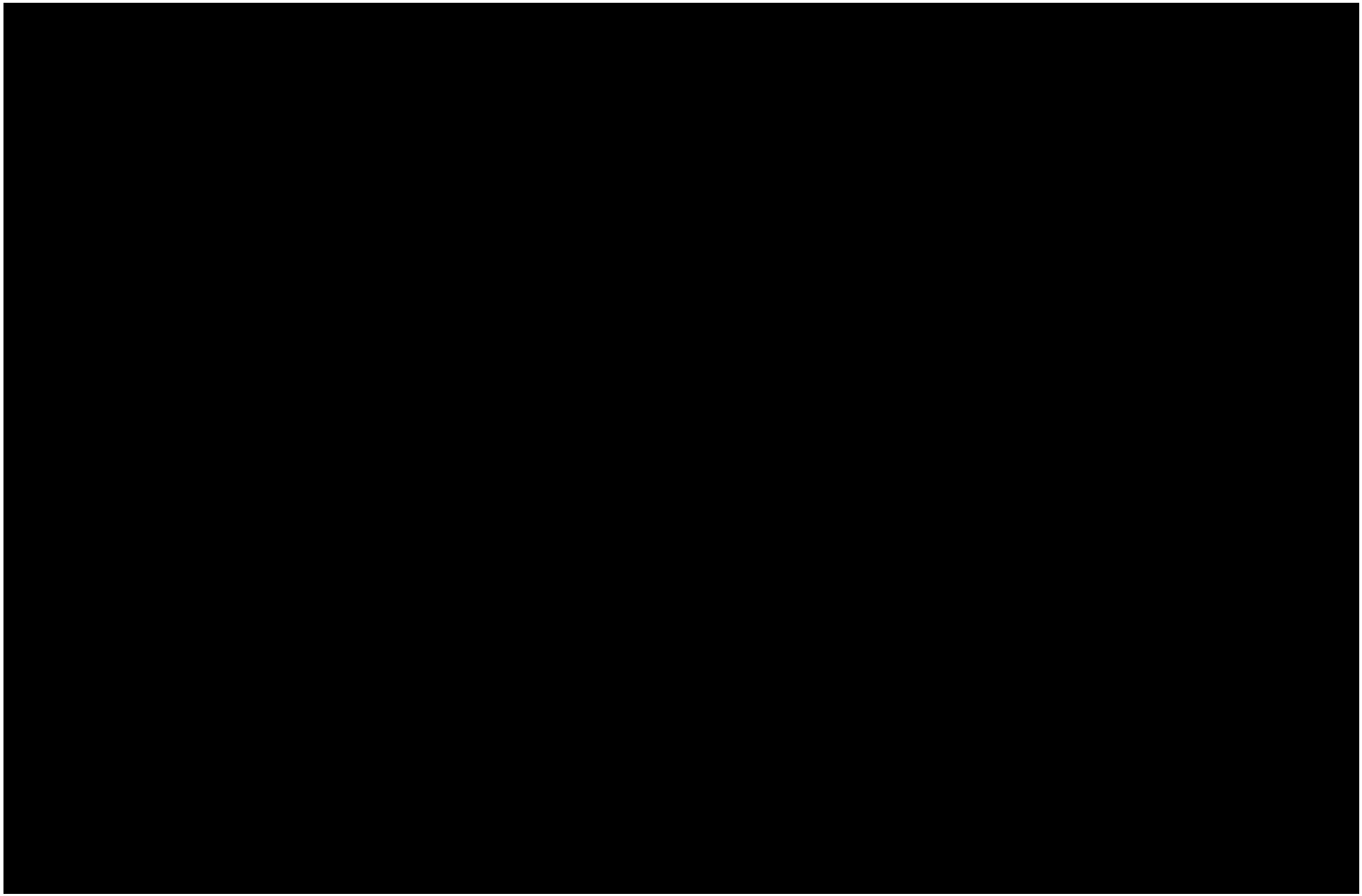
29 To be performed at Screening, every 2 cycles until C5, and then may be performed every 24 weeks (+/- 7 days) from C5D1 on or more frequently as clinically indicated.

30 May be performed every 24 weeks (+/- 7 days) from C5D1 or more frequently as clinically indicated.

Table 7: [redacted]







5.0 BACKGROUND AND STUDY RATIONALE

5.1 Background

Gastrointestinal stromal tumors (GISTs) arise primarily through constitutive activation of the receptor tyrosine kinases KIT or PDGFRA, with approximately 75% of GISTs harboring gain-of-function mutations in KIT (Heinrich 2003; Hirota 1998). These primary activating mutations generally cluster into KIT exons 9 and 11. Exon 9 encodes a portion of the extracellular domain, and mutations in this region induce a conformation change that induces receptor activation.

The more prevalent exon 11 mutations disrupt the secondary structure of the auto-inhibitory juxtamembrane (JM) domain, thus favoring the active kinase conformation (Corless 2011). The discovery that the tyrosine kinase inhibitor (TKI) imatinib inhibits KIT (Heinrich 2000; Tuveson 2001) transformed the clinical management of GIST (Demetri 2002). Nonetheless, most imatinib-treated patients ultimately relapse due to outgrowth of clones with secondary, drug-resistant KIT mutations (Chen 2004; Wardelmann 2006). Secondary mutations typically occur in the adenosine triphosphate (ATP) binding pocket encoded by exons 13 and 14, and the activation loop (A-loop) encoded by exons 17 and 18 (Heinrich 2006). The challenge of treating imatinib-resistant GISTs is compounded by mutational heterogeneity, as patients can harbor multiple different secondary mutations in distinct tumor lesions, or even within different regions of the same lesion (Wardelmann 2006).

GIST patients with imatinib-resistant tumors are treated with the second-line treatment sunitinib, which potently inhibits KIT ATP-pocket mutants (Heinrich 2008). However, sunitinib is ineffective against A-loop mutants, which account for 50% of imatinib-resistance mutations (Demitri 2006; Nishida 2009). This may explain why overall response rates (ORRs) in GIST patients are low (7%) and median progression-free survival (PFS) is short (6.2 months) (Demitri 2006; Heinrich 2008). Regorafenib was recently approved as third-line therapy, but also shows only moderate activity, with an ORR of 4.5% and median PFS of 4.8 months (Demitri 2013). The KIT inhibitory properties of regorafenib have not yet been analyzed extensively, but both clinical and initial preclinical data suggest a limited spectrum of sensitive KIT mutants (George 2012; Serrano-Garcia 2013; Plexxikon data on file). Thus, additional agents are needed to overcome resistance mutations in KIT, in particular those in the A-loop. Ponatinib, which inhibits KIT exon 11 primary mutants and a range of secondary mutants within the A-loop, was studied as potential fourth-line therapy in GIST patients and showed limited, preliminary activity as a third-line treatment (Garner 2014).

PLX9486 was developed to cover mutations in exon 17 and 18, which are not well inhibited by current mutant kit-kinase inhibitors and thus afford a potential source of clonal survival. In addition, PLX9486 maintains potent activity on primary KIT mutants in exons 8, 9, and 11.

5.2 Nonclinical Pharmacodynamics

The biochemical and cell based assays data described in the sections below demonstrate the potency of PLX9486 against imatinib-resistant KIT mutants. These in vitro studies have been validated in vivo, using models that rely on activated KIT readouts.

5.2.1 [redacted]

[redacted]

Table 8: [redacted]

[redacted]

[redacted]

Table 9: [redacted]

[redacted]

5.2.2 In Vivo Pharmacodynamics

PLX9486 was tested in KIT-D816 dependent splenomegaly mouse model, in mastocytosis model harboring mKIT-D814Y mutation, and in a human GIST PDX model harboring activating mutations in KIT kinase that confer resistance to imatinib.

5.2.2.1 BaF3 Splenomegaly Models

A BaF3 cell line expressing KIT-D816V was used in the splenomegaly model to evaluate the in vivo potency of PLX9486 and to establish a pharmacokinetic/pharmacodynamic (PK/PD) relationship. When injected into the tail veins of nude mice, the KIT-D816V/BaF3 cells migrate to the spleen and proliferate to cause a marked splenomegaly over the course of 2 weeks. The in vivo proliferation of the cells and appearance of splenomegaly are directly dependent on the activity of the stably expressed KIT-D816V and can be blocked by oral administration of compounds that are effective KIT-D816V inhibitors. On Day 1, mice were injected intravenously with KIT-D816V BaF3 cell suspension. On Days 7–13, mice were dosed with vehicle or PLX9486 by oral gavage. At the end of study, PLX9486 (administered by oral gavage) demonstrated dose-dependent efficacy. The estimated daily AUCs at ED_{50}, ED_{85}, and ED_{90} were 1650, 19,000, and 36,000 ng•hr/mL, respectively (Figure 1). The estimated exposure to achieve 50% inhibition of BaF3 splenomegaly ($AUC_{0\text{-}24}$ = 1650 ng•hr/mL) is used as the denominator in calculations of exposure multiples to relate PK from other studies and in predicting a minimum efficacious dose. $AUC_{0\text{-}24}$ values between 19,000 and 36,000 ng•hr/mL define the target exposure range for PLX9486 for tumors expressing oncogenic KIT mutations.

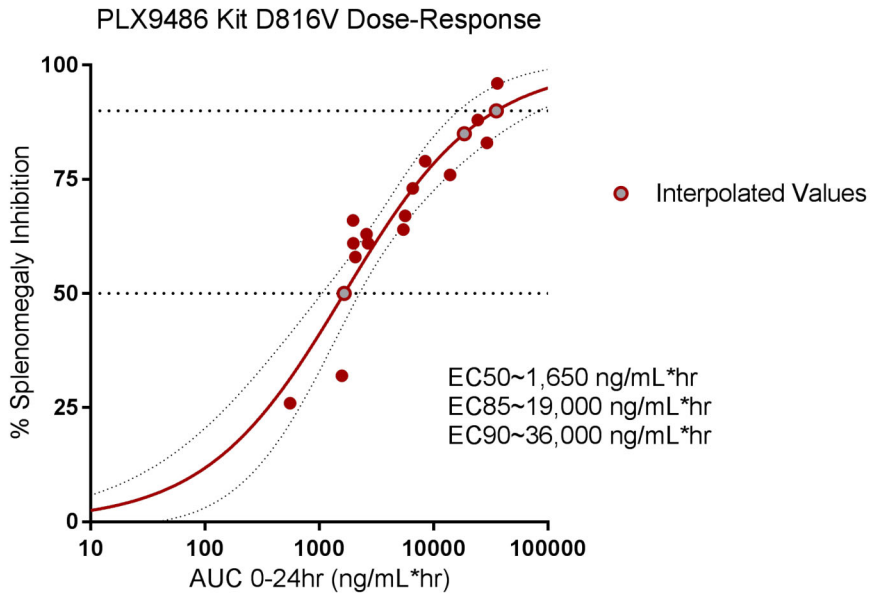


Figure 1: Inhibition of KIT-D816V in the BaF3 Splenomegaly Model

5.2.2.2 [redacted]

[redacted]

Figure 2:

5.2.2.3

Figure 3:

Two follow-up studies (EXP-17-AF0623 and EXP-17-AF0624) evaluated the efficacy of PLX9486 at 2 dose levels (4 and 40 mg/kg) to establish an exposure-response relationship. Mice treated with the lower dose of PLX9486 (4 mg/kg) achieved 63% tumor growth inhibition compared with vehicle-treated mice (Figure 4); the corresponding $AUC_{0\text{-}24}$ was 1090 ng•hr/mL. PLX9486 administered at the higher dose (40 mg/kg) resulted in 44% tumor regression, with 3 of 10 mice demonstrating a nearly complete response (Figure 4). The corresponding $AUC_{0\text{-}24}$ was 11,300 ng•hr/mL.

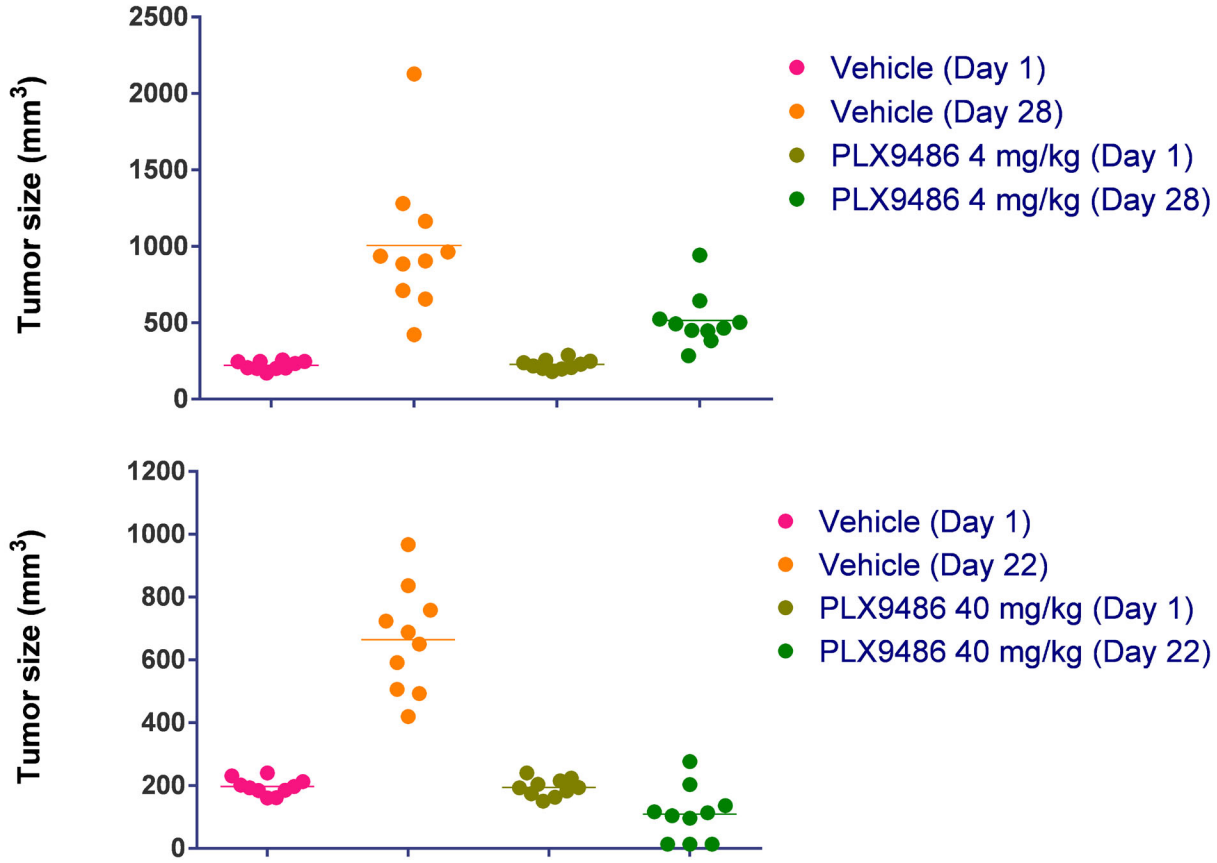


Figure 4: **Human GIST PDX Tumor Growth Inhibition by PLX9486 at 4 and 40 mg/kg Dose Levels**

Please refer to the Investigator's Brochure for updated information and detailed description of the nonclinical pharmacology data.

5.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.4 [redacted]

[redacted]

[redacted]

5.5 Clinical Experience with PLX9486

The oncology study described in this protocol (PLX121-01) is 1 of 2 clinical trials of PLX9486 conducted to date. The other study, PLX121-02, enrolled healthy normal volunteers to investigate the effect of food on 3 dose levels of the drug.

5.5.1 Study PLX121-01: Preliminary Results

The study described in this protocol, PLX121-01, is a 2-part Phase 1b/2a trial to assess the safety, PK, PD, and preliminary efficacy of PLX9486 as a single agent and when used in

combination with PLX3397 or sunitinib in patients with advanced solid tumors and in patients with locally advanced, unresectable, or metastatic GIST who have previously been treated with KIT-directed TKI. The phase 1 portion of the study (Part 1) has been completed.

5.5.1.1 Study PLX121-01 Part 1

Twenty-four patients were enrolled among 5 dose-escalation cohorts ranging from 250 mg/day to 1000 mg/day (Table 10). One DLT was observed in the 1000 mg QD cohort (Grade 3 anemia). Table 11 summarizes the Day 1 and Day 15 (steady state) PK results for these cohorts. The data show a modest increase in exposure at steady state between the 250 mg/day dose (AUC_{0-24}=18,500 ng•hr/mL) and the 1000 mg/day dose (AUC_{0-24}=21,500 ng•hr/mL [QD] and 24400 ng•hr/mL [BID]). The difference in exposure between the 1000 mg QD dose and the 500 mg BID dose is not statistically significant. Because AUC_{0-24} at 1000 mg QD reaches the target exposure range (AUC_{0-24} of 19,000 to 36,000 ng•hr/mL) and because a further increase in dose is not expected to significantly improve AUC, 1000 mg QD was selected as the RP2D for single-agent PLX9486. A single DLT (Grade 3 anemia; 1000 mg QD) was reported among the 24 patients.

Table 10: Study PLX121-01 Part 1 Patient Enrollment and DLT Summary

Part 1 Cohort	PLX9486 Dose Level	Number Enrolled	Number of DLTs (Adverse Events)
1	250 mg QD	3	0
2	350 mg QD	4	0
3	500 mg QD	3	0
4	1000 mg QD	7	1[a]
5	500 mg BID	7	0

BID = twice daily; DLT = dose-limiting toxicity; QD = once daily

[a] DLT: Grade 3 anemia.

Table 11: Study PLX121-01 Part 1 (Dose Escalation) Pharmacokinetic Profile of Single-agent PLX9486 in Patients with Advanced Solid Tumors

Dose		C1D1		C1D15 (Steady State)			Accumulation Ratio
		C_{max} (ng/mL)	$AUC_{0-\tau}$ [a] (ng•hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-24} (ng•hr/mL)	
250 mg QD (N = 3)	GeoMean	499	9240	869	716	18500	2.0
	CV%	6.92	8.7	38.4	42.5	43.7	
350 mg QD (N = 4)	GeoMean	348	7200	1010	789	21300	3.0
	CV%	15.0	20.7	27.5	27.9	27.7	
500 mg QD (N = 3)	GeoMean	326	5250	714	462	15400	2.9
	CV%	28.5	37.3	64.9	119	65.8	
1000 mg QD (N = 7)	GeoMean	558	11000	1060	722	21500	2.0
	CV%	28.1	26.3	59	52.3	60.9	
500 mg BID (N = 7)	GeoMean	331	3150	1150	922	24400	ND
	CV%	22.8	23.7	52.4	51.5	52.5	

AUC = area under the curve; BID = twice daily; CV = coefficient of variation; ND = Not determined

[a] AUC_{0-24} for QD dosing, AUC_{0-12} for BID dosing.

5.5.1.2 Study PLX121-01 Part 2b

As of 01 December 2017, 11 patients have been enrolled in the Part 2b of the study (Figure 5), which seeks to determine the MTD/RP2D of PLX9486 when used in combination with PLX3397. No DLTs have been observed to date (Table 12). All 11 patients had a diagnosis of GIST, and all 11 patients received 500 mg of PLX9486 (50% of the phase 1 RP2D) and 600 mg of PLX3397 as a split dose (AM: 200 mg; PM: 400 mg). Four patients were dosed under fasted conditions, and 7 patients were dosed in the fed state. The PK results for the 2 cohorts are summarized separately in Table 13. Comparison with historical data showed no evidence of drug-drug interaction between PLX9486 and PLX3397. Food had a negligible effect on the exposure of PLX9486 both on Day 1 and at steady state. Food increased the exposure of PLX3397 by approximately 2-fold, consistent with the results of a previous single-dose food effect study. No DLTs have been reported among the 11 patients.

Table 12: Study PLX121-01 Part 2b Patient Enrollment and DLT Summary

Part 2b Cohort	PLX9486 Dose Level	Number Enrolled	Number of DLTs (Adverse Events)
1	PLX9486: 500 mg daily; PLX3397 600 daily (fasted)	4	0
2	PLX9486 500 mg daily; PLX3397 600 daily (fed)	8	0

BID = twice daily; DLT = dose-limiting toxicity; QD = once daily

Table 13: Study PLX121-01 Part 2b Pharmacokinetic Profile of PLX9486 in Combination with PLX3397 in Patients with Advanced Solid Tumors

Dose		C1D1		C1D15 (Steady State)			Accumulation Ratio
		C_{max} (ng/mL)	$AUC_{0-\tau}$[a] (ng•hr/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-24} (ng•hr/mL)	
PLX9486 (500 mg, fasted) (N = 4)	GeoMean	384	7810	991	737	20300	2.6
	CV%	34.4	31.6	53.9	45.8	53.2	
PLX9486 (500 mg, fed) (N = 7)	GeoMean	386	7530	914	649	18700	2.5
	CV%	20.6	17.8	33.1	39.3	34.7	
PLX3397 (600 mg, fasted) (N = 4)	GeoMean	766	8430	3090	2140	64000	ND
	CV%	122	87.8	24.5	32.4	22.3	
PLX3397 (600 mg, fed) (N = 7)	GeoMean	2270	16200	5540	3850	112000	ND
	CV%	53.2	51.6	47.2	51.5	49.7	

AUC = area under the curve; CV = coefficient of variation; ND = Not determined

[a] AUC_{0-24} for PLX9486, AUC_{0-12} for PLX3397.

5.5.2 Study PLX121-02: Preliminary Results

Study PLX121-02 was designed to evaluate 3 dose levels of PLX9486 in healthy normal volunteers and to examine the potential for a food effect. Patients received single doses of 250 mg (fed and fasted), 500 mg (fasted), and 1000 mg (fasted). The 250 mg and 500 mg dose levels were evaluated first. Mean AUC_{0-24} was 5,980 and 8,130 ng•hr/mL for the 250 mg (Cohort A) and 500 mg (Cohort B) dose levels, respectively (Table 14). The data indicated a linear but less-than-dose-proportional increase in exposure from 250 mg to 500 mg. Based on this finding and on safety data, the study safety committee decided to escalate to 1000 mg in Cohort C. In that cohort, AUC_{0-24} was 12,600 ng•hr/mL (Table 14). Thus, a dose increase from 500 mg to 1000 mg appeared to result in higher exposure in healthy normal volunteers and supports the selection of 1000 mg as the RP2D in the present oncology study (PLX121-01). Notably, for Cohort A (250 mg), a high-fat meal increased AUC_{0-24} by 69%, from 5,980 ng•hr/mL to 10,100 ng•hr/mL.

Table 14: Study PLX121-02 Pharmacokinetic Profile of PLX9486 in Healthy Normal Volunteers

Parameter	Geometric Mean (CV%)			
	250 mg Fasted (N = 9)	250 mg Fed (N = 9)	500 mg Fasted (N = 9)	1000 mg Fasted (N = 9)
AUC_{0-24} (ng•hr/mL)	5980 (9.8)	10100 (24.0)	8130 (24.3)	12600 (17.5)
AUC_{0-t} (ng•hr/mL)	29100 (44.5)	52900 (47.2)	46800 (41.4)	83200 (26.7)
$AUC_{0-\infty}$ (ng•hr/mL)	30500 (44.9)	55000 (48.4)	52700 (62.0)	87700 (30.1)
C_{max} (ng/mL)	298 (8.1)	603 (33.2)	396 (25.5)	630 (21.9)
t_{max}[a] (hr)	16 (3–24)	16 (6–48)	12 (8–48)	12 (6–24)
$t_{1/2}$ (hr)	48.6 (43.1)	49.1 (52.1)	66.2 (81.9)	71.4 (31.2)
CL/F (L/hr)	8.19 (44.9)	4.54 (48.4)	9.49 (62.0)	11.4 (30.1)
V_Z/F (L)	574 (14.2)	322 (17.9)	906 (35.2)	1170 (22.6)

AUC = area under the plasma concentration-time curve; AUC_{0-24} = AUC from 0 to 24 hours;
AUC_{0-t} = AUC from time 0 to the time of the last quantifiable concentration;
$AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; CL/F = apparent total plasma clearance;
C_{max} = maximum observed plasma concentration; N = number of patients;
$t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of the maximum observed plasma concentration;
V_z/F = apparent volume of distribution during the terminal phase

[a] Median (minimum–maximum).

A total of 27 patients received PLX9486 in this study, which has been completed. No clinically significant adverse events (AEs) were reported. A study report is in progress.

5.6 PLX3397

PLX3397 is an orally administered FMS, KIT, and oncogenic FLT3 kinase inhibitor being developed for several potential oncology indications either as single agent therapy or in combination with other chemotherapeutic agents.

5.6.1 Clinical Experience with PLX3397

As of 31 July 2017, an estimate of 1002 subjects received PLX3397 or placebo in the clinical program across 28 clinical studies. Of these 1002 subjects, 933 were exposed to PLX3397, and 69 were exposed to placebo (the exact number cannot be accurately determined due to the blinded nature of the ongoing study PLX108-10 at the time of this analysis). Of the 933 subjects, 655 were patients treated in the PLX3397 clinical program. Of the 655 patients, 213 patients with solid tumors received PLX3397 as a single agent (which included advanced, incurable, solid tumors; relapsed or refractory Hodgkin's lymphoma; recurrent glioblastoma [GBM]; or progressive castration-resistant prostate cancer [CRPC] with high circulating tumor cell [CTC] counts). Ninety patients received PLX3397 as a single agent for relapsed or refractory acute myeloid leukemia (AML) in PLX108-05 study. One hundred twenty tenosynovial giant cell tumor (TGCT) patients received PLX3397/placebo in Study PLX108-10. Two hundred thirty-two patients received PLX3397 in combination with other therapies (PLX108-07, PLX108-08, PLX108-09, PLX108-14, and in this study [PLX121-01]). Of the 1002 subjects, 266 healthy

subjects have been treated in the PLX3397 clinical program across 12 clinical studies: PLX108-11, PL3397-A-U114, PL3397-A-U115, PL3397-A-U116, PL3397-A-U117, PL3397-A-U118, PL3397-A-U119, PL3397-A-U120, PL3397-A-U121, PL3397-A-U122, PL3397-A-U125, and PL3397-A-U127. Additionally, 32 subjects with hepatic impairment and matching healthy subjects (study PL3397-A-U123) and 40 subjects with renal impairment and control healthy subjects (study PL3397-A-U124) were treated with PLX3397.

Across the clinical program, the most frequent TEAEs (20%) among all treated patients included fatigue, nausea, decreased appetite, diarrhea, vomiting, anemia, constipation, hair color changes (depigmentation), headache, and increased AST. Severe skin reactions including erythema multiforme and drug reaction with eosinophilia and systemic symptoms (DRESS) have been observed in the clinical studies, although a relationship to PLX3397 has not been established. In addition, acute febrile neutrophilic dermatosis has been observed in patients with AML.

The frequency of TEAEs differs with indication (i.e., TGCT, AML, and advanced malignancy), and the combination of PLX3397 with other chemotherapeutic or targeted therapies may increase the risk and/or severity of adverse findings associated with the individual agents. Individual protocols contain details for AE monitoring and dose modification and should be closely followed.

Hepatotoxicity is an important adverse drug reaction. Elevations of liver transaminases and bilirubin have been observed in studies with PLX3397, together with cases of drug-induced cholestasis. Cholestasis has been observed in the first 8 weeks and has generally resolved with treatment discontinuation, but in some patients it has 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. Protocol-defined dose reductions and discontinuations of PLX3397, frequent laboratory monitoring, and reporting of findings must be followed. In addition, rechallenge with PLX3397 should not be attempted without prior discussion with the Sponsor's Medical Monitor.

In uncontrolled clinical studies of single agent PLX3397 and in combination with other anti-cancer agents, bone marrow suppression with leukopenia (neutropenia and/or lymphopenia), anemia, and thrombocytopenia, either alone or with pancytopenia, has been observed. If clinically significant reduction of neutrophils, serum hemoglobin, or platelets counts is observed, the patient should be monitored closely, and protocol-defined dose modification should be followed. Standard-of-care supportive measures should be initiated, including broad spectrum antibiotics, or hematopoietic growth factors, as appropriate.

For full assessment, please refer to the latest version of the IB.

5.7 Sunitinib

Sunitinib is commercially available. It is United States (US) Food and Drug Administration (FDA)-approved for use in patients with GIST who have progressed on or are intolerant to imatinib. Given its spectrum of activity as previously described and in Table 15, it may augment

the spectrum of KIT activity of PLX9486. Please refer to the US Package Insert (USPI) for further prescribing information.

5.8 Rationale for Use of PLX9486 with PLX3397 in GIST and Other Tumors

PLX3397 and PLX9486 have complementary activity against secondary mutations (in exons 13, 14, and 17) and synergistic activity against primary mutations (in exons 9 and 11) of the KIT receptor in patients with GIST (Table 15). The complementary inhibitor profile of both drugs on mutated KIT kinase is exemplified by the PLX9486 activity against exon 17 mutations, which are PLX3397-resistant, and the PLX3397 activity against exon 13/14 mutations, which are PLX9486-resistant. In addition to its activity against KIT, PLX3397 has activity against the CSF1 receptor and oncogenic FLT3-ITD mutations. PLX3397 is otherwise rather selective against the rest of the kinome.

The sequential (first-line imatinib, second-line sunitinib, third-line regorafenib) kinase inhibitor therapy paradigm drives the development of resistance and KIT mutation heterogeneity within a patient. Furthermore, the KIT mutation heterogeneity across patients can reduce overall response rate (ORR) with a fixed single-dose regimen. To date, KIT appears to be the major driver of most GISTs, and resistance invariably involves secondary KIT mutations. A broader and complementary kinase inhibitor therapy potentially increases ORR and patient benefit in GIST.

Table 15: Primary and Secondary Mutations of the KIT Receptor and Sensitivities to Available and Experimental Treatments

Mutations		Sensitivity (nM)				
		Imatinib	**Sunitinib**	**Sorafenib**	**PLX3397**	**PLX9486**
Primary Mutations						
Exon 8	D419DEL	0.55	0.01	0.384	0.09	0.1
Exon 9	Y503A/F504Y	0.14	0.009	0.164	0.03	0.08
Exon 11	W557K558DEL	0.05	0.04	0.073	0.03	0.12
Secondary Mutations						
Exon 13	K642E	0.38	0.37	0.379	0.26	3
Exon 13	V654A	1.3	0.01	0.592	0.48	10
Exon 14	T670I	8	0.01	0.218	0.08	10
Exon 17	D816V	10	10	10	10	0.1
Exon 18	A829P	1.2	0.58	0.113	1.6	0.13

Germ cell tumors: Exon 17 and to a lesser extent exon 11 mutations have been found in germ cell tumors, more in seminoma than non-seminoma (Bagrodia 2016; Coffey 2008; Tate 2005; McIntyre 2005; Babaei 2016). Germ cell tumors are one of the most common solid tumors in young men; Although even in advanced disease chemotherapy may be curative, some 20% to 30% of subjects will relapse (Bagrodia 2016; NCCN 2016). Nearly half of these patients will die of their disease. Therefore, molecularly targeted therapy against tumors with exon 17 or exon 11 mutations with PLX9486 may allow such patients a novel treatment option.

Multiple other solid and hematologic malignancies have also been associated with KIT mutations such as melanoma, AML, and others (Ashman 2013; Babaei 2016).

Mastocytosis: Mastocytosis is classified was classified as a myeloproliferative neoplasm according to the World Health Organization (WHO) in 2008, but now is a distinct entity in the new WHO classification of myeloid neoplasms (NCCN 2016; Verstovsek 2012; Arber 2016). Exon 17 mutations (e.g., D816V) have been found mastocytosis and are associated with more aggressive disease (Verstovsek 2012; Babaei 2016). Multiple TKIs have been studied in mastocytosis, especially the more aggressive advanced systemic mastocytosis (ASM). Given the activity against the various exon 17 mutations, PLX9486 may offer a new potential therapy for this disease.

5.9 Rationale for the Starting Dose of PLX9486

The proposed starting dose of PLX9486 is 250 mg/day. Human exposure at this dose is predicted to be considerably below the no observed effect level (NOEL) and no observed adverse effect level (NOAEL) determined in toxicology studies of the compound and yet potentially to be sufficient for pharmacologic effects in the oncology patient population to be enrolled in this trial.

Human equivalent doses (HEDs) were calculated using the NOEL/NOAELs determined in rats and monkeys. In the rat, on the basis of a GLP 28-day repeat-dose toxicology study (EXP-13-AC2043), the NOEL was determined to 1000 mg/kg/day. In the monkey, on the basis of a GLP 28-day repeat-dose toxicology study (EXP-14-AC2060), the NOAEL was determined to be 150 mg/kg/day. Using the standard body surface area-based conversion, the HEDs were 9680 mg/day based on the rat NOEL and 2900 mg/day based on the monkey NOAEL suggesting that the monkey was a more sensitive species than the rat on a mg/kg basis. Applying a safety factor of 10x to the HED at the monkey NOAEL gives a maximum recommended starting dose (MRSD) of approximately 250 mg/day for a 60 kg human. This starting dose has a safety margin of 39 (based on the NOEL for rats) and 11.6 (based on the NOAEL for monkeys).

Efficacy in a mouse BA/F3 splenomegaly model was used to determine the efficacious exposure and PK-PD relationship. The efficacious exposure (AUC_{0-t}) where 50% inhibition was seen was 1740 ng•hr/mL for the splenomegaly models. The efficacious exposure was compared to the NOEL/NOAEL determined for rats and monkeys to estimate the therapeutic window. Using either body surface area scaling or drug exposure comparisons, the safety margin based upon the proposed maximum recommended starting dose (MRSD) in humans ranges from 1.4 to 39. The proposed MRSD of 250 mg/day in humans should represent a dose with limited safety risk and the potential for of target inhibition.

5.10 Potential Risks and Benefits

Please refer to Section 5.4 of the PLX3397 Investigator's Brochure and the PLX9486 Investigator's Brochure for safety data for PLX3397 and PLX9486, respectively.

The known clinical toxicities of PLX3397 may be enhanced or even potentiated by the co-administration of PLX9486. To manage this potential risk, the safety of single-agent PLX9486 is to be evaluated in Part 1 of the study, [redacted]

[redacted]

The preclinical studies conducted to date with PLX9486 have shown changes in clinical chemistries in liver function tests (LFTs), renal function, and hematology. In a second toxicology study in rodents, centrilobular, hepatocellular necrosis was observed at exposure levels most likely reachable at the proposed doses. These liver findings correlated with exposure levels in this updated toxicology study. Drug exposure levels, LFTs, PT/INR, renal function, and hematological parameters will be followed closely in this clinical trial population.

Elevations of liver transaminases and bilirubin have been noted in studies with PLX3397 along with drug-induced cholestasis. Cases of cholestasis have been observed in the first 8 weeks, have generally resolved with treatment discontinuation, and in some cases have been severe. Please refer to the PLX3397 Investigator's Brochure for further information. Based on this information, more frequent safety monitoring is now mandated during the first 8 weeks of study therapy with PLX3397.

Sunitinib is commercially available and approved by the US FDA for use in patients with GIST. Please refer to the USPI for further prescribing information. As sunitinib is associated with increases in hepatic transaminases, patients will be monitored for AEs more closely in the first 2 cycles of the combination with PLX9486. In addition, a baseline assessment of thyroid function and cardiac ejection fraction also will be obtained and investigators will reassess as clinically indicated. Other routine assessments (such as physical examination, vital signs, etc.) will be more closely monitored in the first 2 cycles.

The potential benefit of PLX9486 is to provide clinical responses in patients with KIT mutated GIST harboring exon 17/18 mutations. The potential benefit of the combination of PLX9486 with either PLX3397 or sunitinib is the ability to target both the primary mutations (e.g., exon 11) but also the secondary resistance mutations (e.g. exons 13,14,17,18) simultaneously, thus potentially overcoming the multiple mechanisms of resistance earlier in the course of the disease.

6.0 STUDY OBJECTIVES

6.1 Part 1 (Dose-evaluation Cohort) Objectives

The primary objectives for Part 1 of this study are:

- To evaluate safety and pharmacokinetics of orally administered PLX9486 as single and as multiple doses
- To establish the maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) in patients with advanced solid tumors (including GIST)

The secondary objective for Part 1 of this study is:

- To evaluate the efficacy of PLX9486 in solid tumors as measured by ORR (by RECIST 1.1), duration of response (DoR), and progression-free survival (PFS).

The exploratory objective for Part 1 of this study is:

- To assess biomarkers in peripheral blood, archival tumor tissue, and available tumor biopsies.

6.2 Part 2 (Extension Cohorts) Objectives

The primary objectives for Part 2 of this study are:

- [redacted]
- **Part 2b.** Assess the safety and tolerability of the combination of PLX9486 and PLX3397 and to establish an RP2D of PLX9486 in combination with PLX3397 in patients with advanced solid tumors (including GIST).
- [redacted]
- [redacted]
- **Part 2e.** Assess the safety and tolerability of the combination of PLX9486 and sunitinib and to establish an RP2D of PLX9486 in combination with sunitinib in patients with advanced solid tumors (including GIST).
- [redacted]

The secondary objectives for Part 2 are:

- To determine the pharmacokinetics (PK) of PLX9486 as a single agent and in combination with PLX3397 or sunitinib.
- [redacted]
- To estimate the following:
  - ORR (using RECIST 1.1)
  - CBR (Parts 2b and e)
  - Overall survival (OS) and 12-month OS rate
  - Progression-free survival (PFS) and 6-month PFS rate

- Duration of response (DoR)

The exploratory objectives are:

- To assess biomarkers in peripheral blood and in archival tumor tissue
- To assess tumor response in the Part 2 cohorts by Choi criteria (Choi 2007)

7.0 STUDY DESIGN

7.1 Overview of Study Design

This Phase 1b and 2a, open-label, multicenter study includes a dose-evaluation portion (**Part 1**) in which the safety profile and recommended Phase 2 dose (RP2D) of PLX9486 as a single oral agent administered daily in 28-day dosing cycles will be evaluated in patients with solid tumors (including GIST), followed by signal-seeking extension cohorts (**Part 2**) in which the following will be evaluated:

[redacted]

Part 2b. Open-label, sequential cohort dose-finding study of PLX9486 combined with PLX3397 in up to approximately 30 patients with solid tumors (including GIST) in a 3+3 design.

[redacted]

[redacted]

Part 2e. Open-label, sequential cohort dose-finding study of PLX9486 combined with sunitinib in up to approximately 30 patients with solid tumors (including GIST) in a 3+3 design.

[redacted]

A schematic overview of the study design is presented in Figure 5.

Upon progression with single-agent PLX9486 treatment, a patient from Part 1 of the study may be rolled over to combination treatment of PLX9486 and either sunitinib or PLX3397 at the current dose or recommended phase 2 dose at the discretion of Medical Monitor and Principal Investigator (see Schedule of Events in Attachment 5).

The protocol is being amended (Amendment 7) to optimize the schedule of events and associated patient visits consistent with clinical experience in PLX121-01.

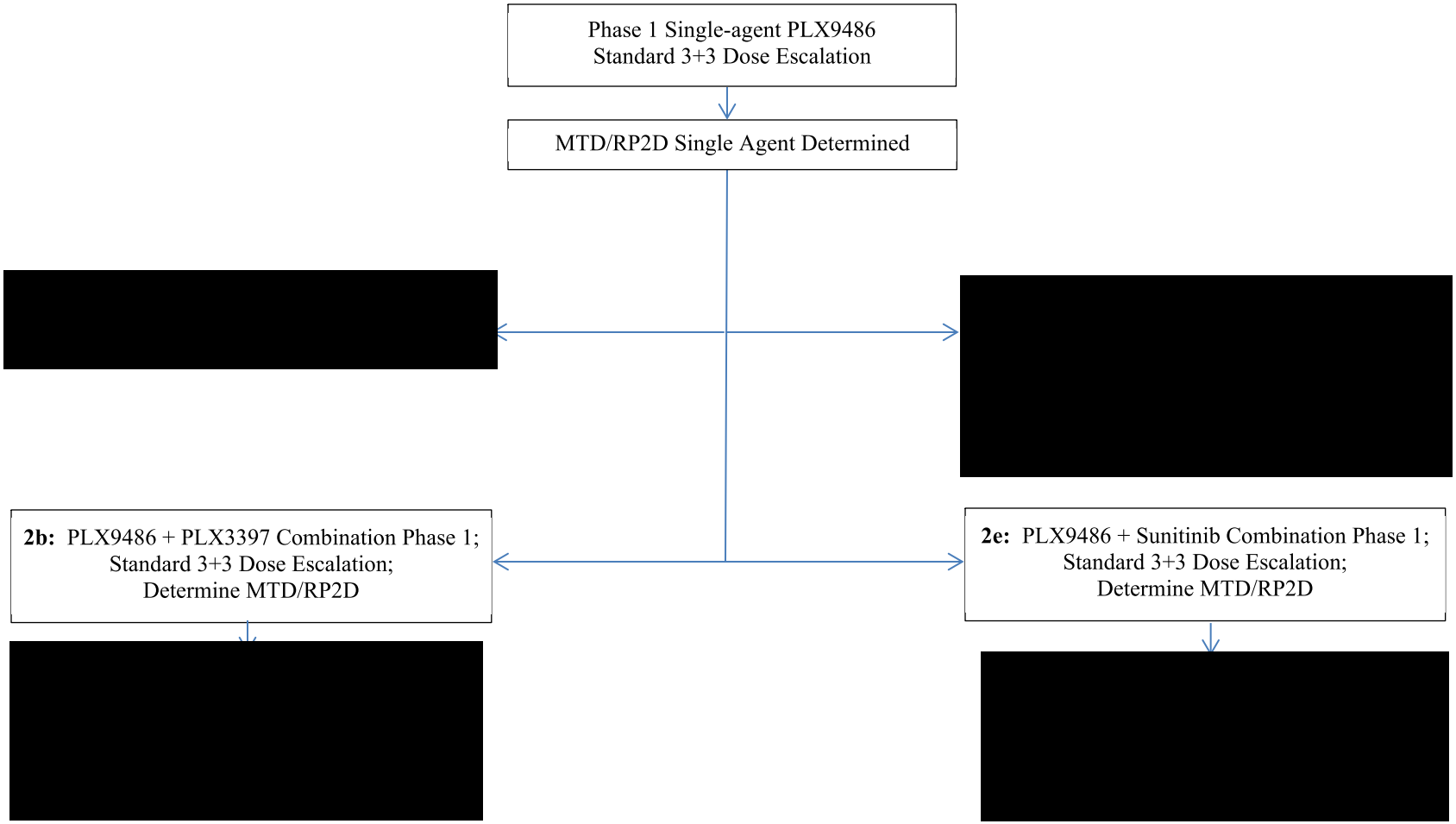


Figure 5: Overview of Study PLX121-01

7.2 Number of Patients

Part 1. Enrollment in the single-agent dose escalation part is planned to be accrued using a standard "3+3" study design and will include up to approximately 30 solid tumor patients to evaluate pharmacokinetics (PK) and observed toxicity. Additional patients may be required, depending on the number of cohorts and evaluable patients needed.

[redacted]

Part 2b. Enrollment in the combination treatment part of the study (i.e., dose-finding for the PLX9486 and PLX3397 combination) is planned to be accrued using a standard "3+3" study design. Part 2b of the study is to include up to approximately 30 solid tumor patients (including GIST patients who have failed approved therapies and at the discretion of the investigator). Additional patients may be required depending on the need for additional cohorts or evaluable patients.

[redacted]

Part 2e. Enrollment in the combination treatment part of the study (i.e., dose-finding for the PLX9486 and sunitinib combination) is planned to be accrued using a standard "3+3" study design. Part 2e of the study is to include up to approximately 30 solid tumor patients (including GIST patients who have failed approved therapies and at the discretion of the investigator). Additional patients may be required depending on the need for additional cohorts or evaluable patients.

[redacted]

7.3 Duration of Study

Screening Period:

- 21 days (with the exception of tumor burden assessment (i.e., CT scan), which may be performed within 28 days of dosing

Treatment Period:

- **Part 1** and **Part 2 (a-f).** 28-day (±7 days) cycles until patient discontinuation or withdrawal or study termination (see Section 10.4)

Follow-up Period:

An end of study visit must occur ≥30 days after the last dose of PLX9486 and prior to starting any new anti-cancer therapy. 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, response, and survival status.

8.0 STUDY POPULATION

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

8.1 Inclusion Criteria

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

1. Male or female ≥18 years old.
2. **Part 1, Part 2b, [redacted] and Part 2e**: Patients with advanced solid tumors who have tumor progression following standard therapy, have treatment-refractory disease, or for whom there is no effective standard of therapy.
3. [redacted]
4. [redacted]

5. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at Screening (≤7 days prior to the first dose of Study drug) and must agree to use an effective form of contraception from the time of the negative pregnancy test up to 6 months after the last dose of study drug. Effective forms of contraception include abstinence, hormonal contraceptive in conjunction with a barrier method, or a double-barrier method. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year.

WOCBP are defined as females who have experienced menarche, have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and are not postmenopausal. All females are considered to be WOCBP except if they have been postmenopausal or surgically sterile for ≥1 year.

6. Fertile men must agree to use an effective method of birth control during the study and for up to 6 months after the last dose of study drug. Male subjects with partners who are either pregnant or become pregnant during the study drug treatment period must agree to continue to use a condom for 90 days after the last dose of study drug.
7. All associated toxicity from previous or concurrent cancer therapy must be resolved (to ≤Grade 1 or Baseline) prior to study treatment administration.
8. Willing and able to provide written informed consent prior to any study related procedures and to comply with all study requirements.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status 0–2.
10. Life expectancy ≥3 months.
11. Adequate hematologic, hepatic, and renal function:
    a. Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9$/L
    b. Hemoglobin >8 g/dL
    c. Platelet count $\geq 100 \times 10^9$/L
    d. AST and ALT ≤upper limit of normal (ULN)
    e. Total bilirubin and direct bilirubin ≤ULN with an exception of patients with confirmed Gilbert's syndrome. For patients with confirmed Gilbert's syndrome, the total bilirubin should be ≤1.5 × ULN.
    f. Creatinine ≤1.5 × ULN or calculated CrCl >60 mL/min (using Cockcroft-Gault formula)
    g. PT (INR) ≤1.5 × ULN

    NOTE: Patients may be transfused prior to study entry.
12. Left ventricular ejection fraction (LVEF) >50% per ECHO or MUGA for patients on the sunitinib arms (Parts 2e and f).

8.2 Exclusion Criteria

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

1. Known or demonstrated wild type KIT or PDGF-R, or known or demonstrated mutations of PDGF-R, SDH, or NF-1 that are causative for the observed malignancy.
2. For Part 1 (phase 1, single agent): Patients with a known or presumed pathogenic KIT exon 13 or 14 resistance mutation.
3. [redacted]
4. Presence of symptomatic or uncontrolled brain or central nervous system metastases. Patients with stable, treated brain metastases are eligible for this trial. However, patients must not have required steroid treatment for their brain metastases within 30 days of Screening.
5. Known or suspected allergy to the investigational agent or any agent given in association with this trial.
6. Clinically significant cardiac disease, defined by any of the following:
   a. Clinically significant cardiac arrhythmias including bradyarrhythmias and/or the need for anti-arrhythmic therapy (excluding beta blockers or digoxin). (Patients with controlled atrial fibrillation are not excluded.)
   b. Congenital long QT syndrome or patients taking concomitant medications known to prolong the QT interval except those required for infections that carry a low risk of QTc prolongation. (See Attachment 4 for a list of drugs known to prolong the QT interval and that carry a risk of inducing torsades de pointes.).
   c. A Fridericia-corrected QT interval of ≥450 msec (for males) or ≥470 msec (for females) at Screening.
   d. History of clinically significant cardiac disease or congestive heart failure >New York Heart Association (NYHA) Class II. Patients must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months.
   e. Uncontrolled hypertension, defined by a systolic blood pressure >150 mmHg or a diastolic blood pressure >100 mmHg that has been confirmed by two successive measurements despite optimal medical management.
   f. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study drug initiation (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before study drug initiation).

7. Inability to take oral medication or significant nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate absorption.
8. Ongoing infection of ≥Grade 2 severity.
9. Non-healing wound, ulcer, or bone fracture.
10. .Patient has known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection or is known to be a carrier of hepatitis B or C. Patients who are positive for hepatitis C virus (HCV) antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible. Prior hepatitis infection that has been treated with highly effective therapy with no evidence of residual infection and with normal liver function (ALT, AST, total and direct bilirubin ≤ULN) is allowed. These patients must be willing to undergo additional testing per local standard of care.
11. Hepatobiliary diseases including biliary tract diseases, autoimmune hepatitis, inflammation, fibrosis, or cirrhosis of liver caused by viral, alcohol, or genetic reasons. Gilbert's disease is allowed if total bilirubin is ≤1.5 × ULN.
12. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
13. Females who are pregnant or nursing.
14. Any psychological, familial, sociological, or geographical condition that could hamper compliance with the study protocol.
15. Strong CYP3A4 inhibitors or inducers within 14 days or 5 drug half-lives of the agent, whichever is longer, of study drug initiation or the need to continue these drugs during this study. (A list of strong CYP3A4 inhibitors and inducers can be found in Attachment 2.)
16. Major surgery or significant traumatic injury within 14 days of Cycle 1 Day 1.
17. History (within 2 years prior to first study drug administration) of another malignancy unless the malignancy was treated with curative intent and likelihood of relapse is small (<5% in 2 years in the judgment of the investigator). Subjects with a history of squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix may be enrolled.
18. Anti-cancer therapy within the period immediately before Cycle 1 Day 1:
    a. Chemotherapy, radiation therapy, small-molecule TKI therapy, or hormonal therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) of Cycle 1 Day 1.
    b. Immune therapy or other biologic therapy (other monoclonal antibodies or antibody-drug conjugates) for the treatment of cancer within 28 days of Cycle 1 Day 1.

9.0 STUDY TREATMENT

9.1 Study Drug Administration

9.1.1 PLX9486

Study drug PLX9486 tablets, 50 mg strength, should be taken orally as defined for each cohort, with approximately 240 mL (8 oz.) of water. Study drug should be taken at approximately the same times of day. Study drug should be swallowed whole and not crushed, chewed, or dissolved in water. A dosing period of up to 1 hour is permissible if required by the number of tablets to be taken or as convenient for the patient.

For patients taking PLX9486 on a BID (twice daily) dosing schedule, the evening dose should be taken approximately 12 hours after the morning dose.

For patients taking PLX9486 on a QD (once daily) dosing schedule, the dose should be taken at the same times of the day and approximately 24 hours apart.

If more than 2 hours have elapsed from the scheduled time of dosing, the dose should be considered missed. Missed doses should be skipped and not taken as a double dose at the next dosing time point. Patients who vomit their dose should be instructed NOT to make up that dose.

Patients may take their PLX9486 medication, whether as a single agent or in combination with PLX3397 or sunitinib. If patients choose to take their medication with food, dosing should occur within approximately 30 minutes of a meal or snack or no later than approximately 1 hour after a meal. As of Amendment 6, patients who were previously instructed to fast for 8 hours prior to dosing are no longer required to fast and may now take their study medication with food.

9.1.2 PLX3397

The study treatment PLX3397 HCl is supplied in 200 mg immediate-release capsules for oral administration.

As of Amendment 6, PLX3397 should be administered once a day, and may be taken with food and can be taken with approximately 240 mL (8 oz.) of water. For subjects instructed to take PLX3397 as BID and on an empty stomach before Amendment 6, the dosing regimen should change to QD going forward and it may be taken with food. The dose should be taken at approximately the same times of the day and approximately 24 hours apart for QD dosing. Study drug should be swallowed whole and not crushed, chewed, or dissolved in water. A dosing period of up to 1 hour is permissible if required by the number of tablets to be taken or as convenient for the patient.

For patients receiving both PLX9486 and PLX3397, the medications may be taken together at the same time and may be taken with food. For patients who are taking PLX9486 and PLX3397 with food, the drugs should be taken within approximately 30 minutes of a meal or snack or no later than approximately 1 hour after a meal. If more than 2 hours have elapsed from the scheduled time of dosing, the dose should be considered missed. Missed doses should be skipped and not taken as a double dose at the next dosing time point. Subjects who vomit their dose should be instructed NOT to make up that dose.

9.1.3 Sunitinib

Sunitinib is commercially available. Please refer to the USPI for further prescribing information. Sunitinib tablets should be taken orally as defined for each cohort, with approximately 240 mL (8 oz.) of water. For patients receiving both PLX9486 and sunitinib, the medications may be taken together at the same time and may be taken with food. For patients who are taking PLX9486 and sunitinib with food, the drugs should be taken within approximately 30 minutes of a meal or snack or no later than approximately 1 hour after a meal. Study drug should be taken at approximately the same times of day. Study drug should be swallowed whole and not crushed, chewed, or dissolved in water. A dosing period of up to 1 hour is permissible if required by the number of tablets to be taken or as convenient for the patient. As of Amendment 6, patients who were previously instructed to fast for 8 hours prior to dosing are no longer required to fast and may now take their study medication with food.

If more than 2 hours have elapsed from the scheduled time of dosing, the dose should be considered missed. Missed doses should be skipped and not taken as a double dose at the next dosing time point. Subjects who vomit their dose should be instructed NOT to make up that dose.

9.1.4 Dosing on PK Sample Collection Days

On PK sample collection days, subjects should be instructed *not* to take their morning dose of PLX9486 and PLX3397 or sunitinib (if applicable) at home before the clinic visit. The time of dosing will be recorded in the clinic. For Part 2b and [redacted], the evening dose of PLX3397 will be taken by the subject at home. On non-PK sample collection days, the subject will administer PLX9486 (and PLX3397 or sunitinib if applicable) independently and record dosing information in the study drug administration diary.

For patients in all parts of the study, one PK sample should be collected at the end of study visit for all patients and if feasible up to 4 additional PK samples may be obtained on Days 3, 7, 10, and 14 after the last dose.

9.2 Dose Levels for Parts 1 and 2

9.2.1 Dose Escalation

9.2.1.1 Part 1: Dose-escalation Cohorts

The initial dosing regimen of PLX9486 will be daily by oral administration. Each treatment cycle will be 28 days.

Cohorts of patients will be enrolled using the standard “3+3” design. The starting dose level of PLX9486 will be 250 mg/day (Cohort 1) using a once-daily (QD) dosing regimen. For higher total daily doses, a split dosing schedule (e.g., twice-daily [BID]) may be used at the current dose level under study or with previously studied daily dose levels. In the absence of Grade ≥2 toxicity that is considered “possibly” or “probably” related to the study agent or dose-limiting toxicity (DLT) and in conjunction with review of the PK data, dose escalation is planned to occur as indicated in Table 16 and as stipulated below.

Table 16: PLX9486 Administration in Part 1: Initial and Potential Dose-escalation Cohorts

Cohort Number	PLX9486 Dose Level (mg/day)[a]	Number and Unit Strength
[redacted]		
4	1000	20 × 50 mg
5	500 (BID)	10 × 50 mg (BID)
6	1500	30 × 50 mg
7	2000	40 × 50 mg

[a] Dosing interval/frequency will be QD unless otherwise specified (e.g., BID dosing).

Further dose escalation or de-escalation may be considered depending upon safety and PK findings and discussion between the Sponsor and the investigators. Dose escalation will continue unless there are dose-limiting toxicities in ≥2 of at least 6 patients (i.e., 33%) in one cohort within the first 28 days.

Also, dose escalation and reduction in smaller increments may be undertaken at any time based upon emerging safety, PK, and PD data.

If a DLT is observed in one patient in the initial cohort of 3 patients, an additional 3 patients will be treated at that dose (see Section 9.3). If DLT is observed in 2 or more patients of either 3 or 6 patients (i.e., ≥33% of patients treated) at a dose level, then a lower dose level of PLX9486 may be introduced unless no further reductions are feasible. If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, and convenience of dosing in approximately 3 to 6 patients treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days.

In addition, if the Study Committee (Section 10.1.1) determines that, in the absence of DLTs, enrollment of additional patients is required in order to better understand PK, safety, or pharmacodynamic markers in specific patient types (e.g., patients with exon 17 mutations), an additional 3 patients may be undertaken at one or more of the dose levels already studied or currently being studied. Alternatively, a split dosing schedule (e.g., BID) may be studied at the current dose level under study or previously studied daily dose levels. Should more than 3 patients be accrued to a dose level for reasons other than DLT/toxicity, the decision to escalate further may be made after the first 3 patients clear the DLT window period after review of the available data by the Study Committee.

Once the safety and tolerability of a dose level have been established by all patients enrolled into the dose level cohort and treated for at least 28 days, intra-patient dose escalation to that dose level will be permitted for patients at lower dose levels who have not experienced a Grade 3 or higher treatment-related toxicity that has not resolved. Additional PK samples may be requested for patients who dose escalate. In addition, additional PK samples may be requested for patients who experience a SAE, DLT, or adverse event of special interest (AESI).

9.2.1.2 Part 2: Extension Cohorts

[redacted]

Part 2b. Cohorts of patients will be enrolled using the standard "3+3" design. The PLX9486 dose escalation may follow the pattern established in Part 1, starting at ≤50% of the MTD/RP2D established in Part 1. In the absence of Grade ≥2 toxicity that is considered "possibly" or "probably" related to the study agent and in conjunction with review of the pharmacokinetic data, dose escalation in Part 2b is planned to occur as indicated in Table 17.

Table 17: PLX9486 and PLX3397 Administration in Part 2b: Initial and Potential Dose-escalation Cohorts

Cohort Number	PLX9486 Dose Level (mg/day)[a]	PLX3397 Dose Level (mg/day)
1	Approximately 50% of Part 1 RP2D	600 (200 mg in AM and 400 mg in PM)
2	Approximately 100% of Part 1 RP2D	600 (200 mg in AM and 400 mg in PM)
3	100% of Part 1 RP2D	400 mg QD (Cycles 1 and 2)
		600 mg QD (Cycle 3 +)[b]
4 +	TBD[c]	TBD[c]

RP2D = recommended phase 2 dose; TBD = to be determined

[a] PLX9486 administered once-daily (QD) or for higher total daily doses, as split doses (e.g., twice-daily [BID]).

[b] At the discretion of the investigator and in the absence of clinically significant drug-related toxicity (Section 9.3) during Cycles 1 and 2.

[c] Based on a review of the data by the Study Committee.

Dose escalation will continue unless there are DLTs in ≥2 of 6 patients in one cohort within the first 28 days of continuous dosing.

Further dose escalation and reduction in smaller increments may be undertaken at any time based upon emerging safety, PK, and PD data. Dose adjustments may also include increasing the number of patients at a given dose level as a result of the review of safety and PK data by the Sponsor and investigators. In addition, alternative dosing schedules may be explored, such as continuous dosing followed by a rest period, staggered dosing of the agents, etc., depending on the safety, PK, or PD-generated data, as well as data from other ongoing PLX3397 studies.

If a DLT is observed in one patient at a given cohort, an additional 3 patients will be enrolled into the cohort. If DLT is observed in ≥2 of at least 6 patients (i.e., ≥33%) at a dose level, then a lower dose level of PLX9486 may be introduced to the combination regimen. If no DLT is

observed, the recommended dose for further evaluation may be established based on toxicity, PK, and convenience of dosing in approximately 3 to 6 patients treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days.

In addition, if the Study Committee (Section 10.1.1) determines that, in the absence of DLTs, enrollment of additional patients is required in order to better understand PK, safety, or pharmacodynamic markers in specific patient types (e.g., patients with exon 17 mutations), an additional 3 patients may be undertaken at one or more of the dose levels already studied or currently being studied. Alternatively, a split dosing schedule (e.g., BID) may be studied at the current dose level under study or previously studied daily dose levels. Should more than 3 patients be accrued to a dose level for reasons other than DLT/toxicity, the decision to escalate further may be made after the first 3 patients clear the DLT window period after review of the available data by the Study Committee.

Once the safety and tolerability of a dose level of PLX9486 in combination with PLX3397 have been established by 3 to 6 patients treated for 28 days (one cycle), intra-patient dose escalation to the next dose level may be permitted for patients at lower dose levels who have not experienced a Grade 3 or higher treatment-related toxicity that has not resolved.

Part 2e. Cohorts of patients will be enrolled using the standard "3+3" design. The PLX9486 dose escalation may follow the pattern established in Part 1, starting at 50% of the MTD/RP2D established in Part 1. In the absence of Grade ≥2 toxicity that is considered "possibly" or "probably" related to the study agent and in conjunction with review of the pharmacokinetic data, dose escalation in Part 2e is planned to occur as indicated in Table 18.

Table 18: PLX9486 and Sunitinib Administration in Part 2e: Initial and Potential Dose-escalation Cohorts

Cohort Number	PLX9486 Dose Level (mg/day)[a]	Sunitinib Dose Level (mg/day)
1	Approximately 50% of Part 1 RP2D	25
2	100% of Part 1 RP2D	25
3	100% of Part 1 RP2D	37.5

RP2D = recommended phase 2 dose

[a] Dosing interval/frequency will be QD unless otherwise specified (e.g., BID dosing).

Dose escalation will continue unless there are dose-limiting toxicities in ≥2 of 6 patients in one cohort within the first 28 days of continuous dosing.

Further dose escalation and reduction in smaller increments may be undertaken at any time based upon emerging safety, PK, and PD data. Dose adjustments may also include increasing the number of subjects at a given dose level as a result of the review of safety and PK data by the Sponsor and investigators. In addition, alternative dosing schedules may be explored, such as continuous dosing followed by a rest period, staggered dosing of the agents, etc., depending on the safety, PK, or PD-generated data.

If a DLT is observed in one patient at a given cohort, an additional 3 patients will be enrolled into the cohort. If DLT is observed in ≥2 of at least 6 patients (i.e., ≥33%) at a dose level, then a lower dose level of PLX9486 may be introduced to the combination regimen. If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, and convenience of dosing in approximately 3 to 6 patients treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days.

In addition, if the Study Committee (Section 10.1.1) determines that, in the absence of DLTs, enrollment of additional patients is required in order to better understand PK, safety, or pharmacodynamic markers in specific patient types (e.g., patients with exon 17 mutations), an additional 3 patients may be undertaken at one or more of the dose levels already studied or currently being studied. Alternatively, a split dosing schedule (e.g., BID) may be studied at the current dose level under study or previously studied daily dose levels. Should more than 3 patients be accrued to a dose level for reasons other than DLT/toxicity, the decision to escalate further may be made after the first 3 patients clear the DLT window period after review of the available data by the Study Committee.

Once the safety and tolerability of a dose level of PLX9486 in combination with sunitinib have been established by 3 to 6 patients treated for 28 days (one cycle), intra-patient dose escalation to the next dose level may be permitted for patients at lower dose levels who have not experienced a Grade 3 or higher treatment-related toxicity that has not resolved.

9.2.2 Dose Escalation Rules

Dose escalation 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 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 less than one-third of evaluable patients in a given cohort experiences a DLT (e.g., DLTs in 0 of 3 or ≤1 of 6 patients), escalation will proceed to the next higher dose level.
- If a DLT is observed in one-third (e.g., 33%) 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 MTD will have been exceeded.
- The highest dose level at which 0 or 1 of 6 experience 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 escalations decisions made by the Sponsor, and investigators and study staff from all participating sites.
- If ≥2 patients in one cohort experience ≥Grade 2 toxicities that are considered possibly or probably related to PLX9486, PLX9486 combined with PLX3397, or PLX9486 and sunitinib within the first 28 days, the study committee will determine the dose escalation increment after review of the safety, PK, and PD data.

9.2.3 Dose De-escalation for PLX9486

For patients receiving PLX9486 (single agent or in combination), dose de-escalation will be in decrements 100 mg per dose for a BID dosing schedule or 200 mg per dose for a QD dosing schedule. Examples of these dose reductions are provided in Table 19 and Table 20.

Table 19: PLX9486 Examples of Dose Reductions for the 500 mg BID Dosing Cohorts

Dose Level	When
500 mg BID	Starting dose
400 mg BID	1st dose reduction
300 mg BID	2nd dose reduction
200 mg BID	3rd dose reduction
Off study	4th dose reduction required

BID = twice daily

Table 20: PLX9486 Examples of Dose Reductions for the 1000 QD Dosing Cohorts

Dose Level	When
1000 mg QD	Starting dose
800 mg QD	1st dose reduction
600 mg QD	2nd dose reduction
400 mg QD	3rd dose reduction
Off study	4th dose reduction required

QD = once daily

Dose reductions should be discussed with the Sponsor's Medical Monitor. Please refer to Section 9.4 for further instructions.

9.2.4 Dose De-escalation for PLX9486 combinations

Combination with PLX3397: If ≥2 of the first 6 patients who receive the first dose level in Part 2b experience a protocol-defined DLT, the administration of PLX9486 and PLX3397 will be considered too toxic and dosing will be reconfigured.

PLX3397 dose de-escalation will be in decrements of 200 mg per day. Examples of these dose reductions are provided in Table 21.

Table 21: PLX3397 Examples of Dose Reductions for the 600 mg Daily Dosing Cohorts

Dose Level	When
600 mg	Starting dose
400 mg	1st dose reduction
200 mg	2nd dose reduction
Off study	3rd dose reduction required

Combination with sunitinib: If ≥2 of the first 6 patients who receive the first dose level in Part 2e experience a protocol-defined DLT, the administration of PLX9486 and sunitinib will be considered too toxic and dosing will be reconfigured as follows:

- Hold sunitinib for ≥Grade 3 drug related AEs
  - First occurrence:
    - Hold drug until AE ≤Grade 1 for non-hematologic events or AE ≤Grade 2 for hematologic events. Resume at same dose level if at 37.5 mg dose.
    - For Grade 3 treatment-related AE, dose reduce to 25 mg if at 37.5 mg or resume at reduced dose of 25 mg.

    - For Grade 4 treatment-related AE, if at 25 mg dose level, hold sunitinib until AE ≤Grade 1 for non-hematologic events or AE ≤Grade 2 for hematologic events, then resume at 25 mg dose level or discontinue sunitinib

- Second occurrence:
    - Hold sunitinib until AE ≤Grade 1 for non-hematologic events or AE ≤Grade 2 for hematologic events. If at 37.5 mg, dose reduce to 25 mg, and if at 25 mg, discontinue sunitinib

9.2.5 Dose Re-escalation after a Dose Reduction

In general, dose re-escalation is not performed in subjects who have had a dose reduction. However, for a subject receiving combination therapy with PLX9486 and sunitinib, re-escalation to the original dose level is permitted at the discretion of the investigator and after discussion with the medical monitor if the subject has not experienced any treatment-related non-hematologic AE or a Grade ≥2 hematologic AE during the previous cycle at the reduced dose level.

9.3 Definitions of Dose-limiting Toxicity

Dose-limiting toxicities (DLTs) are defined as AEs that occur during Cycle 1, are classified as possibly or probably related to the study drug, and meet one of the following CTCAE v4.03 criteria below. DLTs will be evaluated for each cohort and for each dosing schedule. Toxicities that occur during Cycle 2 or later will be reviewed, and their impact on dose-escalation and dosing frequency will be assessed.

In each cohort, to maximize safety, there will be a 24-hour delay between the first subject enrolled and later subjects enrolled. .

Subjects who are considered in dose-escalation decisions are not allowed dose reductions during the DLT assessment window. Subjects who withdraw from the study prior to completing Cycle 1 for any reason other than a DLT will be replaced. Patient numbers must not be re-used.

A subject who experiences a DLT may remain in the trial and continue receiving study drug at a lower dose if the investigator deems the potential benefit outweighs the risk and that the subject is not eligible for, and/or interested in, an alternative therapy after consultation with the Medical Monitor.

Hematologic Toxicities

- Grade 4 neutropenia lasting >7 days
- Grade ≥3 neutropenia with fever
- Grade 4 thrombocytopenia
- Grade ≥3 thrombocytopenia lasting more than 7 days or associated with clinically significant bleeding
- Grade 4 anemia

Other Toxicities

- Any ≥Grade 3 (AE or laboratory) toxicity despite adequate supportive care/medical management except for the following:
  - Grade ≥3 nausea, vomiting, or diarrhea that resolves to Grade ≤2 within 72 hours, with or without medical intervention or prophylaxis because this would not be considered treatment-limiting in an oncology population
  - Grade 3 fatigue that resolves to ≤Grade 2 within 14 days because this would not be considered treatment-limiting in an oncology population
  - Grade ≥3 asymptomatic changes in alkaline phosphatase, hypomagnesemia, hyperglycemia, or hypophosphatemia that is felt by the investigator to be clinically insignificant
  - Grade 3 asymptomatic increases in transaminases (AST, ALT) confirmed upon repeat testing which resolves to ≤Grade 2 within <5 days
- Any other Grade ≥3 toxicity (except those noted above) for which the Principal Investigator or Sponsor deems further dose escalation inappropriate

For both **Part 1** and **Parts 2b** and **2e**, in the absence of a DLT, patients must complete the first cycle of treatment (28 days) in order to be considered evaluable for DLT. Patients who discontinue for any reason other than a DLT or Grade ≥2 toxicity and have received less than 21 of 28 days of dosing will not be considered evaluable for DLT and will be replaced; however, their data will be reviewed by the study committee and a decision will be made based on their review.

9.3.1 Dose-limiting Toxicity Resulting in Death

In the event of a fatal DLT that is possibly or probably attributed to study drug, further accrual to that dose level will be suspended pending review by the Study Committee. The Study Committee (see Section 10.1.1) will review the available data regarding the event and provide recommendations.

9.4 Dose Modification Guidelines and Stopping Rules

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. Table 22 summarizes the guidelines for dosage modification (including stopping rules) for PLX9486–related toxicities as well as guidelines for their management. Dose reductions for PLX9486 should occur in decrements of 200 mg per day and for PLX3397 should occur in decrements of 200 mg/day, depending on the toxicity grade, as noted in Table 21. Table 23 summarizes the guidelines for dosage modification (including stopping rules) for PLX3397-related toxicities (excluding liver function abnormalities) and guidelines for their management. Table 24 summarizes the guidelines for PLX3397 dosage modifications (including stopping rules) for liver function abnormalities, and Table 25 provides additional liver evaluations for the management of liver function abnormalities.

Dose reductions of one or both study drugs will be made based on the known toxicity of PLX3397 and on the specific toxicity of PLX9486, and will be made only after decision by the Sponsor's medical monitor in discussion with the investigator(s). The dose modification guidelines in Table 22 are applicable to all parts of the study. Dose modifications of sunitinib should follow the USPI, as well as the guidance below.

If a stable combination dose of PLX9486 and PLX3397 is unattainable, dosing will be halted and a new dose configuration with a lower dose of PLX3397 (e.g., 600 mg PLX3397 and 150 mg PLX 9486) will be developed. For the combination parts of the study (Part 2b and [redacted]), if one study drug needs to be temporarily discontinued due to an adverse event, then both drugs need to be discontinued until the adverse event resolves per the dose modification guidelines. If one study drug needs to be permanently discontinued, then both study drugs must be permanently discontinued and the patient taken off-study.

If a stable combination dose of PLX9486 and sunitinib is unattainable, dosing will be halted and a new dose configuration with a lower dose of sunitinib (e.g., 25 mg sunitinib and 150 mg PLX 9486) will be developed. For the combination parts of the study (Part 2e and [redacted]), if one study drug needs to be temporarily discontinued due to an adverse event, then both drugs need to be discontinued until the adverse event resolves per the dose modification guidelines. If one study drug needs to be permanently discontinued, then both study drugs must be permanently discontinued and the patient taken off-study.

These parameters are only a guide and are not intended to supersede the clinical judgment of the treating physician. The dose modification/reduction guidelines are for clinically significant toxicities that are at least possibly related to study drug administration. Definitions of "clinically significant" and "related" will be made based on the judgment of the investigator and the case discussed with the Medical Monitor as needed. All adjustments should be made in consultation with the Medical Monitor. 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.

Table 22: Recommended PLX9486 Dose Modifications (Including Stopping Rules)

All Drug-Related Toxicities	Frequency	When to Hold or Stop	When to Restart Dose[a]
Grade 3 or 4 neutropenia	1st Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, resume at same dose.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
Grade 3 or 4 febrile neutropenia	1st Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC ≥1 × 10^9/L and T ≤38°C in ≤7days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
	2nd Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC ≥1 v 10^9/L and T ≤38°C, reduce dose by an additional 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
	3rd Appearance	Discontinue permanently; provide growth factor support	N/A

All Drug-Related Toxicities	**Frequency**	**When to Hold or Stop**	**When to Restart Dose[a]**
Grade 3 or 4 thrombocytopenia without bleeding	1st Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If recovered to PLT $\geq 75 \times 10^9$/L $\leq$7 days, resume at same dose.
			If not recovered to PLT $\geq 75 \times 10^9$/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If recovered to PLT $\geq 75 \times 10^9$/L in $\leq$7 days, reduce dose by 1 dose level.
			If not recovered to PLT $\geq 75 \times 10^9$/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If recovered to PLT $\geq 75 \times 10^9$/L in $\leq$7 days, reduce dose by 1 dose level.
			If not recovered to PLT $\geq 75 \times 10^9$/L after 7 days, discontinue permanently.
	4th Appearance	Discontinue	N/A
Grade 3 or 4 thrombocytopenia with bleeding	1st Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L and bleeding stops	If recovered to PLT $\geq 75 \times 10^9$/L and bleeding stopped $\leq$7 days, reduce by one dose level. If not recovered to PLT $\geq 75 \times 10^9$/L and bleeding continues discontinue permanently.
Other Grade 3 toxicities (excluding trans-aminase increases)	1st Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered $\leq$5 days, resume at same dose.
			If symptoms persist for >5 days despite supportive management, reduce by 1 dose level.
	2nd Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered $\leq$5 days, reduce dose by 1 dose level.
			If symptoms persist for >5 days despite supportive management, discontinue permanently.
	3rd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Other Grade 4 toxicities (excluding trans-aminase increases)	1st Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered <5 days, reduce by 1 dose level.
			If symptoms persist for $\geq$5 days despite supportive management, discontinue permanently.
	2nd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A

All Drug-Related Toxicities	Frequency	When to Hold or Stop	When to Restart Dose[a]
Transaminase increases	• ALT or AST >8 × ULN • ALT or AST >5 × ULN for more than 2 weeks • ALT or AST >3 × ULN and Total bilirubin >2 × ULN or INR >1.5 (in absence of anticoagulation) • ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).	Immediately hold dose and discuss with Medical Monitor. Institute close monitoring. Any decision to restart after transaminases return to baseline must be discussed with the Medical Monitor.	N/A
QTcF >500 msec or 60 msec increase from baseline verified on repeat ECG	First appearance	Interrupt study drug until resolved.	Upon recovery to QTc ≤500 ms (Grade ≤2), restart at a reduced dose (at least one dose level). Permanently discontinue study drug if the QTc interval remains >500 ms and increased >60 ms from pretreatment values (after controlling cardiac risk factors for QT prolongation e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias)[b].

Note: The guidelines in this table apply to all parts of the study.

[a] See Section 9.2 for dose levels.

[b] QTc: Only one dose reduction is permitted per patient. Prior to and following treatment initiation or after dose modification of study drugs for QTc prolongation, evaluate ECG and electrolytes (including potassium, magnesium, and calcium) after 15 days, and monthly thereafter or more often as clinically indicated.

Reductions or interruptions of PLX3397 for toxicity may take place at any time during the study according to the guidelines in Table 23, Table 24, and Table 25. Dose reduction/interruption guidelines for hematologic and nonhematologic treatment-related AEs are based on severity. Dose interruptions can be implemented at the discretion of the treating Investigator to manage intolerable or clinically significant toxicity. If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study drug delay, with the exception of PK

assessments, which should be deferred until treatment is resumed. Interruptions due to toxicity lasting >14 days require treatment discontinuation unless the medical monitor approves continuation.

Table 23: Recommended PLX3397 Dose Modifications (Including Stopping Rules and Excluding Transaminase Increases)

All Drug-Related Toxicities	Frequency	When to Hold or Stop	When to Restart Dose[a]
Grade 3 or 4 neutropenia	1st Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, resume at same dose.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
	4th Appearance	Discontinue	
Grade 3 or 4 febrile neutropenia	1st Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC ≥1 × 10^9/L and T ≤38°C in ≤7days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
	2nd Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC ≥1 × 10^9/L and T ≤38°C, reduce dose by an additional 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
	3rd Appearance	Discontinue permanently; provide growth factor support	N/A
Grade 3 or 4 thrombocytopenia without bleeding	1st Appearance	Interrupt until PLT ≥75 × 10^9/L	If recovered to PLT ≥75 × 10^9/L ≤7 days, resume at same dose.
			If not recovered to PLT ≥75 × 10^9/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until PLT ≥75 × 10^9/L	If recovered to PLT ≥75 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to PLT ≥75 × 10^9/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	Interrupt until PLT ≥75 × 10^9/L	If recovered to PLT ≥75 × 10^9/L in ≤7 days, reduce dose by 1 dose level.

All Drug-Related Toxicities	Frequency	When to Hold or Stop	When to Restart Dose[a]
			If not recovered to PLT ≥75 × 10^9/L after 7 days, discontinue permanently.
	4th Appearance	Discontinue	
Grade 3 or 4 thrombocytopenia with bleeding	1st Appearance	Interrupt until PLT ≥75 × 10^9/L and bleeding stops	If recovered to PLT ≥75 × 10^9/L and bleeding stopped ≤7 days, reduce by one dose level. If not recovered to PLT ≥75 × 10^9/L and bleeding continues discontinue permanently.
Other Grade 3 toxicities (excluding trans-aminase increases)	1st Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered ≤5 days, resume at same dose.
			If symptoms persist for >5 days despite supportive management, reduce by 1 dose level.
	2nd Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered ≤5 days, reduce dose by 1 dose level.
			If symptoms persist for >5 days despite supportive management, discontinue permanently.
	3rd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Other Grade 4 toxicities (excluding trans-aminase increases)	1st Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered <5 days, reduce by 1 dose level.
			If symptoms persist for ≥5 days despite supportive management, discontinue permanently.
	2nd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
QTcF >500 msec or 60 msec increase from baseline verified on repeat ECG	First appearance	Interrupt study drug until resolved.	Upon recovery to QTc ≤500 ms (grade ≤2), restart at a reduced dose (at least one dose level). Permanently discontinue study drug if the QTc interval remains >500 ms and increased >60 ms from pretreatment values (after controlling cardiac risk factors for QT prolongation e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias)[b].

Note: The guidelines in this table apply to all parts of the study.

[a] See Section 9.2 for dose levels.

[b] QTc: Only one dose reduction is permitted per patient. Prior to and following treatment initiation or after dose modification of study drugs for QTc prolongation, evaluate ECG and electrolytes (including potassium, magnesium, and calcium) after 15 days and monthly thereafter or more often as clinically indicated.

Table 24: PLX3397 Dose Modification Guidelines for Liver Function Abnormalities or Bilirubin Increases

Toxicity Grade CTCAE v0.4	Initial Action	Outcome	Action
ALT or AST Grade 2 (>3–5 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor weekly[b] Check for changes to medications and for symptoms	Resolution to Grade 0–1 or baseline (no bilirubin increase)	Restart on resolution Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Grade 3 ALT or AST increase (>5–20 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor 2x/week[b] Check for changes to medications and for symptoms	Resolution to Grade 0–1 or baseline (no bilirubin increase) within 14 days	Restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
		ALT and AST not decreasing within 14 days of holding study drug	Proceed to liver evaluation as outlined in Table 25. Restart only on resolution to Grade 0–1/baseline at 1 dose lower (reduce by one 200 mg capsule); For max AST or ALT >8 × ULN, consult with medical monitor prior to re-start
Grade 4 ALT or AST (>20 × ULN)	Discontinue treatment Monitor 2x/week until resolution to Grade 2 Follow-up until resolution Grade 0–1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined in Table 25. If clear confirmed alternate cause, restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Any grade ALT or AST increase[a] with any bilirubin increase or signs of hypersensitivity	Discontinue treatment Monitor 2x/week until resolution to Grade 2 Follow-up until resolution Grade 0–1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined in Table 25. If clear confirmed alternate cause, restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)

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

[a] An increase in bilirubin is defined as all of the following: total bilirubin >ULN, total bilirubin >20% above baseline, and direct bilirubin is >ULN. If all of these conditions are met, then bilirubin is considered increased and should be immediately re-checked. PLX3397 treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.

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

Table 25: PLX3397 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 d.	Contact Medical Monitor.
We request that cases be discussed with the Medical Monitor as defined in the protocol whenever investigational product is being held for liver function test abnormality.	

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

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

Sunitinib Dose Modification Guidelines:

For all sunitinib drug modifications, see Section 9.2.4. For further guidance, consult the package insert.

9.4.1 Dose Interruptions

Dose interruptions for Grade 2 toxicity for up to 1 week can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. No dose reduction is required when resuming treatment.

Dose interruptions in the middle of a treatment cycle will not affect the cycle and day count on the schedule of assessments. For example, if study drug(s) is (are) held on Cycle 1 Day 10, the following day should still be called Cycle 1 Day 11. If a dose interruption occurs at the

beginning of a new cycle, then the new cycle and day count will begin when study drug is restarted. For example, if study drug is held at the Cycle 2 Day 1 visit, then the day that the patient does resume dosing will be called Cycle 2 Day 1.

9.4.2 Holding of Study Drug

Study drug (PLX9486, PLX3397, and sunitinib) should be held at least 3 days prior to local radiation therapy either for pain palliation or to control slowly progressive disease. Study drug may be resumed 7 days after the completion of radiation therapy at the earliest provided that radiation related skin changes, if any, have resolved. Any AE related to radiation treatment that occurs up to and including 21±7 days after administration of the last dose of study drug must be reported following instruction specified in Section 13.2.

9.5 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 eCRF, including the reason for treatment, generic name of the drug, dosage, route, and start and stop dates of administration.

Of the five major CYP isoforms, 3A4 may be involved in metabolism of PLX3397, with possibly CYP1A2 playing a minor role. PLX3397 is an inhibitor of CYP2C9, CYP2C19, and CYP3A4 in the range of 1 to 30 μM. Until information regarding exposure toxicity and exposure-response relationships are available with PLX3397, concomitant CYP3A4 inhibitors and inducers should be administered with caution, in the event they alter the systemic exposure to PLX3397 (see Attachment 2 for a list of common CYP3A4 inhibitors and inducers). PLX3397 is an inducer of CYP2C8 and 3A4. In general, strong inhibitors, substrates or inducers of CYP3A4 should be avoided unless absolutely clinically necessary. These include anticonvulsants, mycin antimicrobials, and antiretrovirals. Some common examples include inhibitors such as erythromycin, verapamil, itraconazole, and inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.

The in vitro analysis of PLX9486 indicates that the drug does not inhibit or induce any of the major CYP enzymes. CYP3A4 appears to be the main CYP enzyme that metabolizes PLX9486. CYP2C8, 2C19 and 2D6 play a minor role in metabolizing PLX9486. It is recommended to avoid concomitant CYP3A4 inhibitors and inducers with PLX9486.

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, the international normalized ratio (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 enrolled in Part 2b and [redacted] are discouraged from taking proton pump inhibitors (PPIs) or other strong anti-acids (e.g., H-2 antagonists), as these may interfere with the reliable identification of the MTD or R2PD for the PLX9486 and PLX3397 combination.

Patients with isolated or locally progressive metastatic disease amenable to local therapy (e.g., Surgery or chemoembolization for an isolated lesion) may continue on study therapy after their procedure if they are deriving clinical benefit in the judgment of the principal investigator. The patient should stop study drug(s) 3 days prior to the procedure and may resume study drug(s) 7 days after the procedure. The principal investigator should discuss the case with the medical monitor prior to the procedure, including any modification to these guidelines.

Please consult the package insert for other information on sunitinib.

9.6 Precautions and Restrictions

This is the first-in-human study for PLX9486; there are no non-medication-related restrictions or precautions for PLX9486.

Because PLX3397 is a substrate for CYP3A4/5 and grapefruit juice is a CYP3A4/5 inhibitor, foods or beverages containing grapefruit should be avoided throughout the study. Concomitant use of food and herbal preparations that are strong CYP3A4 inhibitors or inducers should be avoided while on study as both PLX9486 and PLX3397 are primarily metabolized by CYP3A4. See Attachment 2 for a list of strong CYP34A inhibitors and inducers.

9.7 Management of Clinical Events

All necessary support care shall be available to patients. For dose-modification guidelines, see Section 9.4.

9.8 Blinding and Unblinding

Blinding methods will not be employed; PLX9486, PLX3397, and sunitinib will be administered in open-label fashion.

9.9 Preparation, Reconstitution, and Dispensation

PLX9486, PLX3397, and sunitinib are anticancer drugs and, as with other potential toxic compounds, caution should be exercised when handling PLX9486, PLX3397, and sunitinib. Specific instructions on preparation, reconstitution, and dispensation will be provided in the PLX121-01 Pharmacy Manual.

9.10 Packaging and Labeling

PLX9486 tablets (50 mg strength) are manufactured, packaged and labeled according to GMP and GCP at the following facility:

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

Sunitinib is commercially available. Please refer to the USPI for further information.

9.11 Storage, Handling, and Accountability

PLX9486 tablets and PLX3397 capsules will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature, between 15–30ºC (59–86ºF). Subjects 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.

Sunitinib is commercially available. Please refer to the USPI for further information.

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 eCRF's.

Specific details and instructions on handling and destruction of unused and partially used study drug will be provided in the PLX121-01 Pharmacy Manual.

9.12 Other Protocol-Specified Materials

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

10.0 STUDY CONDUCT

10.1 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: (Emergency Contacts)	[redacted] Plexxikon Inc. 91 Bolivar Drive, Berkeley, CA 94710 Phone: [redacted] (office) Phone: [redacted] (cell) Fax: [redacted] **E-mail:** [redacted]
SAE Reporting Contact:	The investigator will ensure that the SAE reporting form is completed and E-mailed/eFaxed to the following address within 24 hours of learning of the occurrence of any SAE. **SynteractHCR Safety SAE Facsimile** **Fax:** [redacted] **Telephone:** [redacted] **Email:** [redacted]

10.1.1 Study Committee

The Study Committee will consist of the Sponsor's Medical Monitor, Clinical Program Manager, and the Principle Investigators. The committee will review study data prior to dose escalation and advise on study conduct and protocol design. In addition, in the event of a subject death believed to be possibly or probably related to study drug, the committee will review the information and provide a recommendation regarding further enrollment.

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).

10.3 Treatment Group Assignments

This is an open-label, sequential dose-escalation study with extension cohorts. The initial dose level of PLX9486 will be 250 mg/day. Thereafter, dose-escalation groups will occur as described in Section 9.2.1. Extension cohorts will be enrolled in parallel at the RP2D according to inclusion and exclusion criteria (Section 8.1 and Section 8.2). The initial dose of PLX3397 will be 600 mg/day administered BID. Thereafter, dose escalation groups will occur as described in Section 9.2.1.2. For the combination cohort with sunitinib the initial sunitinib dose will be 25 mg/day. Further details may be found in Section 9.2.1.2.

10.4 Withdrawal of Patients from Drug Treatment or from the Study and Patient Replacement

The Plexxikon Medical Monitor will monitor safety data throughout the course of the study. The Medical Monitor will review SAEs within timeframes mandated by company procedures and will review trends, laboratory data, and AEs at periodic intervals 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, adverse event, 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). 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 30 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 adverse event 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.

10.5 Study Compliance

The study drugs PLX9486 and 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.

10.6 Enrollment of Patients

After potential patients have been identified by the site personnel and informed consent has been obtained, the site will inform the Sponsor/Sponsor's representative and a slot will be reserved for the patient. Once all screening assessments are completed, the site personnel will email the Sponsor/Sponsor's representative with the enrollment packet. The Sponsor's medical monitor or designee will review and approve the enrollment (via email typically) and inform the Sponsor's representative that the patient has been approved for enrollment and assign the appropriate dose level. Further information may be found in the study manual.

10.7 Protocol Violations and Deviations

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following categories:

- Enrollment criteria
- Study activities (e.g., missed evaluations or visits, data verification issues)
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay, or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

11.0 STUDY ASSESSMENTS

Event schedules are summarized in Table 1 (Part 1), Table 2 [redacted] Table 3 (Part 2b), Table 4 [redacted] Table 5 [redacted] Table 6 (Part 2e), and Table 7 [redacted]

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 institutional review board (IRB)/independent ethics committee (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 Plexxikon Inc., signed by the appropriate representative, and returned to the investigative site.

Screening procedures are to be performed within 21 days before Cycle 1 Day 1 of study therapy. Each treatment cycle for Part 1, [redacted] 2b, [redacted] 2e, and [redacted] will be 28 days.

Dose interruptions in the middle of a treatment cycle will not affect the cycle and day count on the schedule of assessments. For example, if study drug is held on Cycle 1 Day 10, the following day should still be called Cycle 1 Day 11, etc. If a dose interruption occurs at the beginning of a new cycle, then the new cycle and day count will begin when study drug is restarted. For example, if study drug is held at the Cycle 2 Day 1 visit, then the day that the patient does resume dosing will be called Cycle 2 Day 1.

The end of the study for each patient is defined as the date of the last dose of PLX9486, PLX3397, or sunitinib (see Section 10.4 for reasons for discontinuation or withdrawal of a patient from the study).

11.1 General Guidelines for Performing Study Assessments

The following procedures, on the days scheduled, should be performed *before* the morning dose of study treatment:

- Predose vital signs.
- Predose 12-lead ECG.
- Predose blood sampling (e.g., clinical laboratory tests, PK, PD, circulating DNA).
  Note: All blood sampling should be performed *after* the ECG and assessing vital signs.
- AE assessment.

The following procedures, on the days scheduled, should be performed *after* the morning dose of study treatment:

- Postdose 12-lead ECG.
  Note: Unless otherwise stated, the time points for postdose ECGs have a collection window of ±30 minutes.
- Postdose vital signs.
  Note: The time point for assessing postdose vital signs has a window of ±30 minutes.
- During Cycle 1, the postdose PK sample at Hour 1 has a collection window of ±10 minutes; subsequent collection time points have a window of ±30 minutes.
- AE assessment.

11.2 Study Procedures

11.2.1 Electrocardiograms

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

11.2.2 Tissue Biopsy Samples

Archival 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.

For Part 2 an optional predose and Cycle 2 Day 1 paired tumor tissue biopsy of a progressive lesion may be obtained in patients with accessible tissue. KIT mutation testing of archival tissue and freshly obtained biopsies will be performed at one or more central laboratories. Data will be tabulated and mutation status correlated with response to treatments.

Tissue specimens from all patients at the Screening visit will be collected and retained for future validation of a KIT mutation assay.

At any time during the study, after informed consent has been obtained, the investigator, at their discretion, may obtain a fresh tumor biopsy from a representative lesion. If a biopsy is obtained, a block, partial block, or at least 10 unstained slides should be sent to the sponsor.

11.2.3 Optional Fresh Tumor Biopsy and Circulating Tumor DNA

This may be taken at any time in per the discretion of the investigator and after informed consent is obtained from the patient. All patients will be required to permit exploratory evaluations of their archival tumor tissue whenever archival tissue is available. If >6 months (approximately) have elapsed since the last biopsy, a repeat biopsy/ies of representative lesions (in the judgment of the investigator) are recommended. Patients with biopsy-accessible tumors in Part 2 will also be asked to consider participation in optional exploratory evaluations of paired biopsies. If a fresh paired biopsy is obtained, the biopsies should be from the same lesion if possible/feasible, and preferably from a non-target lesion.

Circulating tumor DNA (ctDNA) will be collected at baseline, every treatment cycle, and at disease progression.

Further handling/shipping instructions may be found in the study manual. Refer also to Section 11.2.2.

11.2.4 [redacted]

[redacted]

11.2.5 Physical Findings

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

11.2.6 Redacted Copies of Reports, Scans, or Photographs for the Sponsor

The sponsor may request redacted copies of study procedures such as pathology reports, scans, or photographs obtained during the study as appropriate.

11.2.7 Pharmacology Assessments

11.2.7.1 Pharmacokinetics

During Parts 1 and 2, blood samples will be obtained to determine the PK of PLX9486 as a single agent and also the PK of the combination of PLX9486 and PLX3397 and of PLX9486 and sunitinib. Once the PK of PLX9486 as a single agent is determined in the fasted state, food effect may be explored.

11.2.7.2 Pharmacodynamics

During Parts 1 and 2, blood samples will be obtained for ctDNA and potentially other exploratory PD markers. Tissue samples will be analyzed for KIT mutations per Section 11.2.2.

11.3 Blood Collection

The estimated volume of blood to be collected at each visit for Part 1 and Part 2 of the study are shown in Table 26. The quantities of blood are within accepted limits of 10.5 mL/Kg or 550 mL (whichever is smaller) per NIH and other published guidelines (DF/HCC 2012; NIHCC 2009; NS LIJ 2013).

Table 26: Potential Blood Sample Volumes Collected in Parts 1 and 2

	Blood Sample Volumes (mL)												
	Screening	Cycle 1						Cycle 2				Cycle 3+	
STUDY DAY► TEST▼	Day –21 to -1	Day 1	Day 2 +1 d	Day 8 ±2 d	Day 15 ±2 d	Day 16 ±2 d	Day 22 ±2 d	Day 1 ±7 d	Day 8 ±2 d	Day 15 ±3 d	Day 22 ±2 d	Day 1 ±7 d	EOS
Hematology	8	8	8	8	8	8	8	8	8	8	8	8	8
Chemistry	8	8	8	8	8	8	8	8	8	8	8	8	8
Coagulation tests	8	8						8				8	8
Blood for Biomarker Assessment (PD)		10			10								
Circulating DNA	40	40			40			40		40		40	40
PK Blood Samples		18	3		18	3	3	3		3		3	15
Total Volume[a,b]	**64**	**92**	**19**	**16**	**84**	**19**	**19**	**67**	**16**	**59**	**16**	**67**	**79**

EOS = end-of-study; PD = pharmacodynamic; PK = pharmacokinetic

[a] The maximal blood volume drawn per day is about 95 mL. The total blood volume drawn over 8 weeks is approximately 462 mL.

[b] Totals represent maximum blood volume drawn for any cohort on study. Depending on cohort enrollment and patient duration on study, blood volume may be less than described above for the 8-week period of Cycle 1 and 2.

11.4 Biomarker Samples and Pharmacogenomics

Baseline subject blood samples (serum, plasma, whole blood) will be obtained for pharmacodynamic and biomarker assessments. These may be repeated at subsequent time points throughout the study. In addition, subjects will be asked to submit archival tumor samples, and may be asked to have subsequent tumor biopsies while on the study. These tumor samples may also be used for pharmacodynamic and biomarker assessments. While some of the assessments are prospectively described in the protocol, new assessment methods may emerge during the study or after it has concluded. Hence some samples may be stored and analyzed at a later date as newer technologies emerge.

Pharmacodynamic and other biomarker samples may be used to identify prognostic or predictive biomarkers. In addition, they may be used to improve the understanding of the biology of the disease under study, the metabolism of the drug, to help identify subjects who may be more or less likely to benefit from the drug, or who may be at risk for potential toxicity from the drug.

Analyses to be done on the samples (blood and tumor) for this study may include, but are not limited to:

- Genetic analyses of tumor tissues for mutations of KIT
- Circulating tumor DNA in blood
- Circulating tumor DNA and tumor biopsy-derived DNA (if available) will be analyzed for KIT exon mutations, PDGF-R, SDH, and NF-1 mutations to determine eligibility for the planned extension cohort.
- Genomic analysis and expression arrays may also be performed for exploratory purposes

The science of biomarkers and assays is always evolving and therefore a definitive list of biomarkers remains to be determined and may include additional markers suggested by preclinical/clinical research or referenced in the literature or other scientific conferences as the science and technology evolve.

Stored samples will only have the patient study number as an identifier, and will not have any patient identifying information such as name, birthdate, etc. Samples will be stored for 3 years after the end of the study, or per local guidelines, and then they will be destroyed.

As part of this study, blood samples will be collected for pharmacogenomics analysis. Where required by local regulations, participation in pharmacogenomic sample collection is optional and will be addressed in a separate Pharmacogenomics ICF at screening. In these regions, subjects who choose not to provide a sample for pharmacogenetic analysis may still participate in the study.

For subjects who participate in pharmacogenetic testing, a blood sample should be collected at the screening visit(s) or as indicated in the schedule of assessments. This sample may be analyzed only for genes suspected to contribute to the safety and efficacy of the study medications. The analysis may also include a comprehensive evaluation of genetic information,

with a particular focus on specific genetic changes considered to potentially predict responsiveness or resistance to treatment.

Results may also provide information on how individuals metabolize and react to the study drug or help to identify subjects who are more or less likely to benefit from the study drugs. The information may be useful to increase the knowledge of differences among individuals in the way they metabolize the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Because emerging information regarding the safety and efficacy of study medications may become available in the future, pharmacogenomic samples may also be banked for possible future research. In all regions, pharmacogenomic sample banking is optional and will be addressed in a separate Pharmacogenomics ICF at screening. Samples will be retained until the DNA has been exhausted or until the sponsor instructs the genotyping contractor to destroy the sample (in accordance with laboratory procedures). During the period of storage, the DNA sample will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time.

The samples will be shipped to a central laboratory for forwarding to analysis laboratory(ies), which has been contracted by the sponsor to process these samples.

In order to ensure subject confidentiality, sample tubes will be identified only by a barcode label. This barcode will be linked to the subject's SID number. Samples will be stored for 3 years after the end of the study, or per local guidelines, and then they will be destroyed.

Sample collection, preparation, handling, storage, and shipping instructions are in the Laboratory Manual.

12.0 STATISTICAL CONSIDERATIONS

12.1 Randomization and Stratification

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

12.2 Populations for Analysis

The primary population for efficacy and safety will consist of the modified ITT population, i.e., patients who receive at least one dose of study drug and have any follow-up data.

The safety analysis population will consist of all patients treated with at least 1 dose of study drug. Safety data will be summarized by dose level, based on the original assigned dose of the study drug.

The efficacy analysis population for the primary and secondary efficacy endpoints will consist of all patients who have taken at least 1 dose of study drug and have had at least 1 post-baseline tumor assessment. Efficacy will be summarized by cohort.

The PK and PD analysis populations will consist of all patients who have received the requisite treatments and have data at the required time points. Any windows for timing of measurements will be specified in the statistical analysis plan.

12.3 Sample Size Considerations

Statistical Considerations: Part 1 follows the traditional 3 + 3 design; Table 27 shows the probability of escalating to the next dose after either 3 or 6 subjects for given true DLT incidence rates.

Table 27: True Incidence of DLTs for Part 1

True Incidence of DLTs	10%	20%	30%	40%	50%	60%	70%
Probability of Escalating the Dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03

The sample sizes of the different parts of the study are based on clinical rather than statistical considerations. The dose escalation cohorts (Part 1 and Parts 2b and 2e) follow a typical 3 + 3 design. Data will be tabulated and evaluated by descriptive statistics.

12.4 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.

12.5 General Methodology

Summary tabulations will be presented for each part of the study 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.

12.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized will be summarized for each part of the study.

12.7 Efficacy Analysis

12.7.1 Dose-escalation Cohorts (Part 1)

Secondary Endpoint:

The secondary endpoint of Part 1 is to evaluate the efficacy of PLX9486 in solid tumors as measured by ORR (by RECIST 1.1), duration of response (DoR), and progression-free survival (PFS). The ORR and the 2-sided, exact binomial 95% confidence interval for the ORR will be estimated. DoR and PFS will be estimated using the Kaplan-Meier method.

Statistical considerations (secondary endpoint): at the RP2D, if the observed overall response rate (ORR) is 17% (1 response of 6 patients), the 2-sided exact binomial 95% confidence interval for the true ORR is (0.4%, 64.1%). If the observed ORR is 33% (2 responses of 6 patients), the corresponding 95% confidence interval for the true ORR is 4% to 78%.

Exploratory Endpoints:

Descriptive statistics will be used to assess biomarkers in peripheral blood, in archival tumor tissue and in available tumor biopsies.

12.7.2 Extension Cohorts (Part 2)

Primary Endpoints:

Clinical Benefit Response (CBR) is defined as SD at 16 weeks + PR + CR.

See Table 28 for variations on sample sizes and response rates.

Parts 2b and 2e: Determine the safety and tolerability and establish the RP2D of PLX9486 in combination with PLX3397 or sunitinib.

Statistical considerations: The sample size of the different arms of the proposed escalation parts of the study were based on clinical rather than statistical considerations. The dose escalation cohorts (Part 1 and 2b and 2e) follow a typical 3 + 3 design. Data will be tabulated and evaluated by descriptive statistics.

Secondary Endpoints:

[redacted]

Statistical considerations (safety and tolerability, CBR, ORR, OS, 12-month OS rate, PFS and 6-month PFS rate, DoR): descriptive statistics. The Kaplan-Meier method will be used to estimate the distributions of PFS, DoR, and OS.

Table 28 below shows 2-sided exact binomial 90% and 95% lower and upper confidence limits (LCL and UCL) for the true response rate given various combinations of sample size and observed response rate.

Table 28: Two-sided Exact Binomial Confidence Limits for the True Response Rate

Sample Size	Number of Responders	Response Rate (%)	Observed CBR Rate			
			90% Confidence Interval		95% Confidence Interval	
			Lower (%)	Upper (%)	Lower (%)	Upper (%)
15	3	20	5.68	43.98	4.33	48.09
	4	26.7	9.67	51.08	7.79	55.10
	5	33.3	14.17	57.74	11.82	61.62
	6	40	19.09	64.04	16.34	67.71
	7	46.7	24.37	70.00	21.27	73.41
	8	53.3	30.00	75.63	26.59	78.73
	9	60	35.96	80.91	32.29	83.66

Exploratory Endpoints:

Parts 2[redacted]. For each part, descriptive statistics will be used to summarize biomarkers in peripheral blood, in archival tumor tissue, and in tumor biopsies.

Tumor response will be evaluated in the Part 2 cohorts by Choi criteria (Choi 2007).

12.8 Pharmacokinetics/Pharmacodynamics/Biomarkers

12.8.1 Pharmacokinetic Analysis

The pharmacokinetic profile of plasma PLX9486 will be analyzed by measurement of area under the plasma concentration-time curve [$AUC_{0\text{-}9}$. $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$ $AUC_{0\text{-}\infty}$], peak concentration (C_{max}), time to peak concentration (T_{max}), and half-life ($T_{1/2}$). The pharmacokinetic profile of plasma PLX3397 in Part 2b and [redacted] will be analyzed by measurement of area under the plasma concentration-time curve [$AUC_{0\text{-}6}$, $AUC_{0\text{-}9}$. $AUC_{0\text{-}t}$], peak concentration (C_{max}), and time to peak concentration (T_{max}).

Dose proportionality following study medication will be explored by analyzing natural log-transformed pharmacokinetic variables, $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$. $AUC_{0\text{-}inf}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate. Dose linearity for $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$. $AUC_{0\text{-}inf}$, and C_{max} will also be explored by a linear model. The food effect of PLX9486 will be evaluated at a later time point.

A potential interaction between the absorption, distribution, metabolism, elimination (ADME) profiles of PLX9486 and PLX3397 and of PLX9486 and sunitinib will be explored by determining the PK profiles of both drugs in the first 28-day dosing cycle.

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

12.8.2 Pharmacodynamic Analysis

Exploratory PD parameters will be analyzed appropriately (if samples are available).

12.8.3 Tissue Evaluation

Exploratory studies as part of this proposal will:

- determine biomarkers of KIT inhibition
- correlate clinical outcomes with response and tumor parameters

Planned biomarkers are listed in Attachment 1.

12.8.4 Blood Biomarker 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.

12.9 Safety Analysis

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

Adverse event terms recorded on the eCRFs will be mapped to prefer 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 subjects), worst reported severity, and relationship to study drug for each preferred term per subject. Serious adverse events 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 4.0) 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 PLX9486 dose.

ECG, weight, and vital signs will also be summarized by changes from baseline to scheduled time points using descriptive statistics.

12.9.1 Part 1

The primary safety objectives of Part 1 are to evaluate the safety of orally administered PLX9486 and to establish the maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) in patients with advanced solid tumors (including gastrointestinal stromal tumor [GIST]).

12.9.2 [redacted]

[redacted]

12.9.3 Part 2b

The primary safety objectives of Part 2b are to assess the safety and tolerability of the combination of PLX9486 and PLX3397 and to establish an RP2D of PLX9486 and PLX3397 in patients with advanced solid tumors (including GIST).

Statistical Considerations: Part 2b follows a modified 3 + 3 design. Table 29 shows the probability of escalating to the next dose after either 3 or 6 subjects for given true DLT incidence rates.

Table 29: True Incidence of DLTs for Part 2b

True Incidence of DLTs	10%	20%	30%	40%	50%	60%	70%
Probability of Escalating the Dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03

12.9.4 [redacted]

[redacted]

12.9.5 [redacted]

[redacted]

12.9.6 Part 2e

The primary safety objectives of Part 2e are to assess the safety and tolerability of the combination of PLX9486 and sunitinib and to establish an RP2D of PLX9486 and sunitinib in patients with advanced solid tumors (including GIST).

Statistical Considerations: Part 2e follows a modified 3 + 3 design; Table 30 shows the probability of escalating to the next dose after either 3 or 6 subjects for given true DLT incidence rates.

Table 30: True Incidence of DLTs for Part 2e

True Incidence of DLTs	10%	20%	30%	40%	50%	60%	70%
Probability of Escalating the Dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03

12.9.7 [redacted]

[redacted]

12.10 Interim Analysis

No formal interim analysis is planned.

13.0 ADVERSE EVENTS

13.1 Definitions

13.1.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject 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. 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, e.g., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE 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 v4.0 criteria.

13.1.2 Serious Adverse Event Definition

A serious adverse event (SAE) is any AE, occurring at any dose and regardless of causality that:

- Results in **death**
- Is **life-threatening**. Life-threatening means that the subject 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 longer than 24 hours or prolongation of existing hospitalization** (see clarification in the paragraph below on planned hospitalizations). An emergency room visit without hospitalization is not considered a hospitalization.
- 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 subject 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 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 subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A severe adverse event 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.

13.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

A subject's AE or SAE can occur from the time the subject signs informed consent until the End of Study visit. Specifically, any AE attributed to a protocol-mandated procedure occurring after the subject has provided informed consent but prior to the first dose of study drug should be recorded as an AE. Adverse events that are not attributed to protocol-mandated procedures occurring after signing of the informed consent but before the first dose of study drug will be reported as medical history.

All AEs spontaneously reported by the subject 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 adverse event 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 13.1.2, must be reported by the investigator to Plexxikon or CRO designee by faxing or e-mailing 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 30 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 Plexxikon Product Safety within 1 working day. ALL SAEs and deaths must be reported whether or not considered causally related to the study drug. The SAE Form, created specifically by Plexxikon, will be provided to each clinical study site. The information collected will include a minimum of the following: subject 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 Plexxikon. SAEs reported to Product Safety must match the data provided on the CRF.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the subject 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 4.0, 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 subject'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.

13.2.1 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.

13.3 Monitoring of Adverse Events and Period of Observation

All AEs will be recorded from the time the consent is signed through 30 days after last dose of study drug or prior to initiating new anticancer therapy, whichever occurs first. AEs that occur after signing informed consent but before first dose of study drug that are not related to a protocol-mandated procedure will be recorded as medical history only. AEs occurring as a result of a protocol-mandated procedure after signing of informed consent will be recorded as AEs.

All SAEs will be evaluated from the time the consent is signed through 30 days after last dose of study and prior to starting any new anticancer therapy. Any SAE occurring within this window must be reported to Plexxikon or its designee within 24 hours of the knowledge of the event.

13.4 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to Plexxikon Product Safety as described in the Safety Monitoring Plan The pregnancy must be followed through final outcome (i.e., beyond delivery) for SAEs.

13.5 Worsening of Cancer

Clear progression of neoplasia should not be reported as an adverse event or serious adverse event. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not qualify for a serious adverse event. Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should be reported as an adverse event or serious adverse event as appropriate.

13.6 Adverse Events of Special Interest

AESIs should be reported as SAEs as outlined in Section 13.2. At present, there are no AESIs identified for this study.

14.0 ADMINISTRATIVE REQUIREMENTS

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (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 IB.

14.2 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 subject. Study data will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. Plexxikon 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.

14.3 Electronic Case Report Form Completion

Plexxikon 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 electronic case report forms (eCRFs) for the subjects for which they are responsible.

eCRFs will be completed for each study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject'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 subjects for which he is responsible.

Plexxikon, 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.

14.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Plexxikon will be followed, in order to comply with GCP guidelines. Plexxikon, or a CRO designee, will be responsible for study monitoring.

All information recorded on the eCRFs for this study must be consistent with the subject'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 subject confidentiality is maintained.

There will be no Data and Safety Monitoring Committee (DSMC) for this study. Patient updates, safety issues, and study progress will be discussed during regularly scheduled teleconferences with investigators. In addition, investigator feedback will be solicited for all dose escalation decisions. Data listings will be provided for review in advance of a dose escalation decision, and Plexxikon and each of the site investigators will determine and agree upon a plan to proceed with dose escalation based on the safety and PK data.

14.5 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The study must fully adhere to the principles outlined in *Guideline for Good Clinical Practice, ICH Tripartite Guideline, January 1997*, or with local law if it affords greater protection for the patient. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent form, advertisements (if applicable), written information given to the subjects (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.

14.6 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the subject 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).

14.7 Subject Confidentiality

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

14.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Plexxikon, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not be made without agreement of both the investigator and Plexxikon. 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 subjects. Plexxikon, 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 subjects, the investigator will contact Plexxikon, or a CRO designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

14.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Plexxikon 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.

14.10 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 subject, and amount returned to Plexxikon, or a CRO designee, (or disposal of the drug, if approved by Plexxikon) will be maintained by the clinical site. Plexxikon or its CRO designee will review drug accountability at the site on an ongoing basis.

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

14.11 Product Complaints

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

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

14.12 Closure of the Study

The study will be considered closed after the last subject has progressed, died, withdrawn from study treatment, or been lost to follow-up, whichever occurs first.

The Sponsor currently has no plans to provide PLX9486 or the combination of PLX9486 + PLX3397 to study subjects after the close of the study or earlier subject withdrawal. However, the Sponsor will evaluate the appropriateness of continuing to provide PLX9486 or the combination of PLX9486 + PLX3397 to study subjects after evaluating study data pertaining to the primary efficacy outcome measure and safety. These analyses may be conducted prior to study completion. For subjects who are demonstrating a clinical benefit at the end of this trial, the possibility of continuing their treatment in this or a roll-over protocol may be considered.

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 Plexxikon, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Plexxikon by the terminating party.

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

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enter subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or un-evaluable data
- Determination 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 Plexxikon once the site's participation in the study has concluded.

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

14.13 Record Retention

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 Plexxikon notified.

15.0 USE OF INFORMATION

All information regarding PLX9486 and PLX3397 supplied by Plexxikon 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 Plexxikon. It is understood that there is an obligation to provide Plexxikon with complete data obtained during the study. The information obtained from the clinical study will be used towards the

development of PLX9486 and PLX3397and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Plexxikon, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement (CTA).

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ATTACHMENT 1: LABORATORY TESTS

Hematology

- Hemoglobin and hematocrit
- White blood cell count with differential
- Platelet count
- RBC Count

Blood Chemistry

- Sodium
- Potassium
- Chloride
- CO2
- Calcium
- Magnesium
- Phosphorus
- Glucose
- Blood urea nitrogen
- Creatinine
- Uric acid
- Total protein
- Albumin
- Total and direct bilirubin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (AP)
- Lactate dehydrogenase (LDH)

Coagulation Tests

Prothrombin time (PT)/International normalized ratio (INR)
Partial thromboplastin time (PTT)

Urinalysis (microscopic)

- pH
- Protein/albumin
- Glucose/sugar
- WBCs
- Nitrites
- Ketones/acetone
- Hemoglobin/blood
- Casts or other microscopic findings

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

Plasma Samples for PK

Blood Response Biomarkers (Tumor DNA)

Paired Biopsy Tissue Response Biomarkers

RNA sequencing

Tumor DNA sequencing/Tumor Gene Expression Analysis

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 PLX9486 treatment.

ATTACHMENT 2: STRONG CYP3A4 INHIBITORS AND INDUCERS AND CYP3A4 SUBSRATES

Strong Inhibitors	Strong Inducers	Substrates
indinavir	carbamazepine	Alfuzosin
nelfinavir	efavirenz	Alprazolam
ritonavir	nevirapine	Budesonide
clarithromycin	phenobarbital	Carbamazepine
itraconazole	phenytoin	Colchicine
ketoconazole	pioglitazone	Cyclosporine
nefazodone	rifabutin	Dexamethasone
erythromycin		Disopyramide
grapefruitjuice		Ergotamine
verapamil		Fluticasone
suboxone		Lovastatin
diltiazem		Methylprednisolone
		Midazolam
		Pimozide
		Quinidine
		Repaglinide
		Rifabutin
		Sildenafil
		Simvastatin
		Tadalafil
		Triazolam
		Vardenafil
		Vinblastine
		Vincristine

Source: IUPUI Division of Clinical Pharmacology, The Flockhart Table: P450 Drug Interaction Table, 2016

ATTACHMENT 3: DRUGS CLEARLY ASSOCIATED WITH THE RISK OF TORSADES DE POINTES (TDP) AND QT PROLONGATION

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

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 self-care. Totally confined to bed or chair
5	Dead

* As published in Oken 1982

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

ATTACHMENT 5: SCHEDULE OF ASSESSMENTS FOR PATIENTS FROM PART 1, [redacted] WHO HAVE CLINICAL PROGRESSION AND HAD PLX3397 OR SUNINITIB ADDED TO TREATMENT

Table 31: Trial Flow Chart – Patients from Part 1, [redacted] Who Have Clinical Progression and Had PLX3397 or Suninitib Added to Treatment

STUDY DAY► / EVENT▼	Cycle 1 After TKI Added					Cycle 2 After TKI Added				Cycle 3+ After TKI Added	Other	EOS[27]	FU[28]
	Day 1	Day 8 ±2 d	Day 15 ±2 d	Day 16 ±1 d	Day 22 ±2 d	Day 1 ±7 d	Day 8 ±2 d	Day 15 ±3 d	Day 22 ±2 d	Day 1 ±7 d			
Informed Consent													
Archival Tissue [1]													
Optional Fresh Tumor Biopsy[2]													
Demographics and Medical History													
Prior Treatment for Primary Malignancy													
Height													
Weight	X	X	X		X	X		X		X		X	
Physical Exam[3]	X[4]	X	X		X	X		X		X		X	
Hematology[5]	X[4]	X	X		X	X		X		X		X	
Chemistry[6]	X[4]	X	X		X	X		X		X		X	
Coagulation Tests (PT/INR and PTT)	X[4]					X		X		X		X	
Tumor Markers[7]	X[4]					X		X		X		X	
Urinalysis[8]	X[9]	X	X		X	X		X		X		X	
12-Lead ECG[10]	X[11]		X[11]			X[11]				X[11]		X	
Vital Signs[12]	X[13]	X	X	X	X[13]	X		X		X		X	
Blood for PK[14, 15]	X		X	X	X	X		X		X		X	
Blood for PK (safety)[16]										X[16]			
Serum Pregnancy Test[17]												X	

Table 31: Trial Flow Chart – Patients from Part 1, [redacted] Who Have Clinical Progression and Had PLX3397 or Suninitib Added to Treatment, continued

STUDY DAY▶ / EVENT▼	Cycle 1 After TKI Added					Cycle 2 After TKI Added				Cycle 3+ After TKI Added	Other	EOS[27]	FU[28]
	Day 1	Day 8 ±2 d	Day 15 ±2 d	Day 16 ±1 d	Day 22 ±2 d	Day 1 ±7 d	Day 8 ±2 d	Day 15 ±3 d	Day 22 ±2 d	Day 1 ±7 d			
ECOG Performance Status	X[4]	X	X		X	X			X	X		X	
Blood for Biomarker Assessment (PD)[15, 18]	X		X										
Circulating DNA[15, 19]	X		X			X		X		X		X	
PLX9486 Administration[20]	X[21]	X[22]	X[21]	X[21]	X[21]	X[21]		X[21]		X[21]	Daily[22]		
Add-on PLX3397, Sunitinib, or Other KIT-directed TKI[29]	X[21]	X[22]	X[21]	X[21]	X[21]	X[21]		X[21]		X[21]	Daily[22]		
Radiographic Assessment of Tumor Burden (CT or MRI Scan)[23]										~Every 2 cycles	~Every 3 cycles after Cycle 12		
Compliance via Diary Review & Accountability		X	X	X		X[24]		X[24]		X[24]		X[24]	
Concomitant Medications[25]	X	X	X	X	X	X		X		X		X	
Adverse Events	X[26]	X	X[26]	X[26]	X[26]	X[26]		X[26]		X[26]		X	
Phone Interview													X

CBC = complete blood count; CXDX = Cycle number Day number; CT = computed tomography; ECG = electrocardiogram; EOS = end of study; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; FU = follow-up; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; PT = partial thromboplastin; PTT = partial thromboplastin time; QTcF = QT interval corrected for heart rate using Fridericia's method; SAE = serious adverse event; TKI=tyrosine kinase inhibitor

1 Analysis for SDH, PDGF-R, and NF-1 mutations.
2 May be taken at any time from screening onward.
3 Complete physical exam at Screening and End of Treatment only. All other physical examinations may be abbreviated and symptom-directed.
4 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation tests, and tumor markers do not need to be repeated if these assessments from Screening occurred within 2 days of C1D1 **unless a change in status is suspected**.
5 Hematology evaluation must include CBC with differential and platelet count. Complete list of required tests are found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria.

Table 31: Trial Flow Chart – Patients from Part 1, [redacted] Who Have Clinical Progression and Had PLX3397 or Suninitib Added to Treatment, continued

6 Chemistry evaluation must include a complete metabolic panel including liver transaminases. Complete list of required tests are found in Attachment 1 to the protocol. Laboratory values obtained on C1D1 do not have to re-meet eligibility criteria.
7 β-HCG (beta-human chorionic gonadotropin) and AFP (alpha-fetoprotein) should be assessed for germ cell tumors (e.g., seminoma, non-seminoma, etc.) on day 1 of every cycle. Other tumor markers for other malignancies to be performed as per institutional practice guidelines.
8 Urinalysis with urine dipstick is sufficient; if there is significant proteinuria, hematuria, or leukuria, a microscopic examination should be obtained. Complete list of required tests are found in Attachment 1 to the protocol.
9 Not required if Cycle 1 Day1 assessment is less than 7 days from Screening assessment.
10 Standard 12-lead ECG with QTcF calculation. Fridericia's correction is required. QTcF = $(QT)/\sqrt[3]{(RR)}$. All ECGs should be obtained in triplicates (approximately 10 seconds for each ECG over a 5-minute period).
11 C1D1 ECGs will be obtained predose and at 3 hours postdose. C1D15 ECGs will be obtained predose and at 1, 3, 5, 7, and 9 hours postdose. Beginning at C2D1, ECG will be collected before dosing at the start of each cycle (e.g., C3D1, C4D1). All postdose ECGs should be collected at the specified time point ±30 minutes unless otherwise stated.
12 Predose vitals must be obtained on PK days. On non-PK, non-PD days, vital signs do not need to be predose and patients may self-administer PLX9486 at home either prior to or after their clinic visit (if applicable).
13 Vitals to be obtained at 4 hours postdose (±30 minutes).
14 Peripheral blood samples for the PK analysis of PLX9486 will be collected at:
Cycle 1 Day 1 at predose and 1, 3, 5, 7, and 9 hours postdose.
Cycle 1 Day 15 at predose and 1, 3, 5, 7, and 9 hours postdose.
Cycle 1 Day 16 at predose.
Cycle 1 Day 22 at predose.
Cycle 2 Day 1 at predose
Cycle 2 Day 15 at predose.
Cycle 3+ Day 1 at predose.
One PK sample should be collected at the end of study visit for all patients.
All Cycle 1 PK samples should be collected at the specified time points ±10 minutes at the 1 hour sample and ±30 minutes at subsequent time points.
15 Patients must come into the clinic after an overnight fast of at least 8 hours. Patients should remain fasting unless otherwise specified until after the dose of study drug is taken. Note: As of Amendment 6, subjects who were assigned to fast for at least 8 hours prior to dosing are no longer required to fast and may take their study medication with food.
16 Additional peripheral blood samples for PK may be requested for patients who intrapatient dose escalate or who have an SAE. For patients who are able to intrapatient dose escalate to a higher dose level, PK to be obtained at predose and 1, 3, 5, 7, and 9 hours postdose on the first day of dose escalation and on Day 15 after dose escalation. A trough (pre dose) sample should be obtained on day 1 of subsequent cycles after dose escalation (i.e., if they intrapatient dose escalate at Cycle 2, collect the trough PK sample on Day 1 from Cycle 3 onwards). For patients who experience a SAE or AE of special interest, a sample will be requested at the time of the event and the time of the last dose before the PK collection to be noted.
17 Serum pregnancy test must be negative within 7 days prior to C1D1 for women of child-bearing potential.
18 Peripheral blood samples for will be obtained predose. The ±window does not apply to PD samples. PD samples must be obtained on the specified day whenever possible.

Table 31: Trial Flow Chart – Patients from Part 1, [redacted] Who Have Clinical Progression and Had PLX3397 or Suninitib Added to Treatment, continued

19 Whole blood for circulating DNA assessment to be obtained predose.
20 Patients should fast approximately 1 hour before administration and approximately 2 hours after administration of PLX9486, unless otherwise specified.
21 Patients must receive their dose in the clinic. Patients should be instructed not to take their PLX9486 and added TKI dose at home on these visit days that include PK or PD collection. If alternate day dosing is used, patients will be instructed on which days to take PLX9486 (e.g., even or odd numbered days).
22 Patients may self-administer PLX9486 and the added TKI with water at home prior to or after their clinic visit on these days.
23 Screening radiographic assessment of tumor burden may be within 28 days of scheduled C1D1. After C1D1, radiographic assessment of tumor burden will be performed approximately every 2 cycles (e.g., after Cycle 2, 4, 6) or more frequently as clinically indicated. After Cycle 12, radiographic assessment of tumor burden may be performed every 3 cycles (e.g., after Cycle 15, 18, 21). Patients obtaining PET CTs on study do not also need separate CT scans, and disease can be followed via PET CT. The Sponsor may request copies of the scans and reports for purposes of central review.
24 Drug diary to be reviewed and collected. Distribution of new drug diary.
25 Review of concomitant medications must include all medications taken within 28 days prior to Screening.
26 AE monitoring both predose and postdose on these days when PLX9486 is taken in the clinic.
27 This visit must occur ≥30 days **after** last dose of PLX9486 and prior to starting any new anti-cancer therapy.
28 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, response, and survival status.
29 The investigator must consult the medical monitor if they want to use any other TKIs, aside from PLX3397 or sunitinib.