Title	A Phase 1b Study to Assess the Safety of PLX3397 and Paclitaxel in Patients with Advanced Solid Tumors
Protocol Number	PLX108-07
IND Number	105,521
Sponsor	Plexxikon Inc. 91 Bolivar Drive Berkeley, CA 94710, USA
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Date/Version	03 November 2016/Amendment 8

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1.0 SPONSOR SIGNATURE

I have read and approved this protocol.

[redacted]

Medical Monitor/Regional Director Signature

03 NOV. 2016

Date of Signature
(DD Mmm YYYY)

[redacted]

Medical Monitor/Regional Director Name
(print)

2.0 INVESTIGATOR 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.

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

Investigator Signature

Date of Signature
(DD Mmm YYYY)

Investigator Name and Title (print)

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4.0 CONTACTS

4.1 Emergency Contacts

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Email: [redacted]

5.0 LIST OF ABBREVIATIONS

Abbreviation or Term[a]	Definition/Explanation
AE	Adverse event
ADLs	Activities of Daily Living
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_6 (AUC_{0-6})	Area under the concentration-time curve from time zero 6 hours after dosing
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
CSF-1	Colony stimulating factor-1 [also known as macrophage stimulating factor (M-CSF)]
CSF-1R	Colony stimulating factor receptor (also known as Fms)
CTX	Chemotherapy
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCs	Circulating Tumor Cells
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
DFS	Disease-Free Survival
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
ED-50	Effective dose
EORTC	European Organization for Research and Treatment of Cancer
e.g.	Exempli gratia (for example)
FACS	Flow cytometry

Abbreviation or Term[a]	Definition/Explanation
FDA	Food and Drug Administration
Fms	Colony stimulating factor 1 receptor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyltransferase
GLP	Good laboratory practice
HCO_3^-	Bicarbonate
hERG	Human Ether-à-Go-Go
HNSTD	Highest non-severely toxic dose
HPLC	High-performance liquid chromatography
HR	Heart rate
Hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IL-1β	Interleukin-1β
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LD_{50}	Median lethal dose
LDH	Lactate dehydrogenase
MDSC	Myeloid-derived suppressor cell
MEC	Microvascular endothelial cell
MedRA	Medical Dictionary for Drug Regulatory Activities
MMP-3	Matrix metallopeptidase-3
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PDGFR	Platelet derived growth factor receptor
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial remission
PT	Prothrombin time
PTT	Partial thromboplastin time
PTX	Paclitaxel
QC	Quality control

Abbreviation or Term[a]	Definition/Explanation
QD	Once daily
QTcF	Corrected QT interval, Frederica's formula
QOL	Quality Of Life
RBC	Red Blood Cell
RP2D	Recommended Phase 2 Dose
Rx	Treatment
SAE	Serious adverse event
SCF	Stem Cell Factor
SD	Standard deviation or stable disease
STD	Severely toxic dose
T_{max}	Time of maximum observed concentration
TAMs	Tumor-associated macrophages
TEAE	Treatment-emergent adverse event
TKI	Tyrosine Kinase Inhibitor
TTE	Trans-thoracic echocardiogram
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

[a] All of these abbreviations may or may not be used in the protocol.

6.0 STUDY SYNOPSIS

Title	A Phase 1b Study to Assess the Safety of PLX3397 and Paclitaxel in Patients With Advanced Solid Tumors
Study Objective(s)	This trial is designed as a three-part study. **Part 1:** The primary objective is to explore the safety and tolerability of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D. The secondary objectives are to explore the efficacy and pharmacokinetics (PK) of PLX3397 in combination with paclitaxel in patients with advanced solid tumors. **Part 2:** The primary objective is to confirm the safety and tolerability of PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors. The secondary objective is to explore the efficacy of PLX3397 in combination with paclitaxel in patients with advanced solid tumors. **Part 1 and 2:** Exploratory objectives include correlating the change in Colony Stimulating Factor-1 (CSF-1) levels during treatment with specific dose levels of PLX3397 and identifying new biomarkers of clinical activity. **Part 3:** The primary objective is to determine the efficacy of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. The secondary objectives are to explore the effect of PLX3397 on cancer tissue and blood biomarkers and the safety and tolerability of PLX3397 in combination with paclitaxel in this patient population.
Study Design	**Part 1**: This is a nonrandomized, open-label study employing a standard 3+3 dose escalation design to determine the RP2D of PLX3397, a novel inhibitor of the CSF-1 receptor (Fms), when administered in combination with paclitaxel in patients with advanced solid tumors. **Part 2**: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (including all RP2D-treated patients from Part 1 and Part 2). The candidate population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. **Part 3:** This is a nonrandomized, open-label study of PLX3397 600 mg BID administered in combination with paclitaxel in approximately 30 patients. The candidate population will be patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Patients must be resistant or refractory to prior platinum-based standard care systemic regimens or refractory to primary treatment with a platinum-containing regimen. Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms: 1) daily PLX3397 600 mg BID; 2) weekly paclitaxel; and 3) daily PLX3397 600 mg BID and weekly paclitaxel. Cancer tissue (biopsy) for biomarkers will be obtained during Screening and at Cycle 1 Day 28 ± 7 days (Cycle 1 Day 21 to Cycle 1 Day 35). If the second biopsy in Cycle 1 is delayed beyond Day 28, patients will have a Cycle 1 Day 28 visit, during which procedures would be the same as the Cycle 1 Day 22 visit. Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with daily PLX3397 600 mg BID and weekly paclitaxel. Cycle 2 and all subsequent cycles will be 28-day cycles. Blood biomarkers will be obtained prior to treatment on Day 1 of all subsequent cycles and the End-of-Study Visit. Patients will have efficacy assessments every 8 weeks to determine objective response (CR + PR), clinical benefit (CR + PR + SD), progression-free survival (PFS), and time to next treatment.

Number of Patients/Sites	**Part 1:** Enrollment is planned to include approximately 30 patients recruited from approximately 3–4 sites. The total number of patients to be enrolled will depend on the number of cohorts, whether a cohort requires 3 or 6 patients, and whether patients who are not evaluable for DLTs need to be replaced. **Part 2:** Enrollment is planned to include approximately 30 patients (including RP2D-treated patients from **Part 1** and **Part 2**) recruited from 3 sites. **Part 1 and Part 2:** Patients who do not receive the requisite PLX3397 and/or paclitaxel doses in Cycle 1 due to anything other than treatment-related and/or dose-limiting toxicity may be replaced. Patients who experience an allergic reaction to paclitaxel that precludes further dosing (i.e., ≥Grade 3) will be removed from the study and may also be replaced. **Part 3:** Enrollment is planned to include up to approximately 30 patients recruited from approximately 9 sites to accrue 18 patients who can provide pretreatment and end-of-Cycle 1 cancer tissue and are evaluable for determining response using RECIST 1.1 criteria. Patients unable to provide the sequential cancer tissue samples or non-evaluable for response using RECIST criteria will be replaced.
Study Treatments	**Part 1:** PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. The starting dose of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%. Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. One paclitaxel dose may be omitted per cycle by physician discretion after Cycle 1. **Part 2:** PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. The dose of PLX3397 will be the RP2D. There will be no dose escalation. Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. One paclitaxel dose may be omitted per cycle by physician discretion after Cycle 1. **Part 3:** Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms: 1) PLX3397 600 mg BID using a continuous dosing regimen 2) Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes 3) PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with PLX3397. **Part 1, Part 2, and Part 3:** Study treatment will be provided until disease progression, unacceptable or dose-limiting toxicity, death, withdrawal of consent, study termination by Sponsor, or if the Investigator and patient agree that it is in the patient's best interests to discontinue.

Study Procedures	**Part 1:** This nonrandomized, open-label study will employ a traditional 3+3 Phase 1 design, with escalating dosing cohorts of PLX3397 and a fixed dose level of paclitaxel. Each treatment cycle will be 28 days. Dosing of PLX3397 will commence at the 600 mg/day dose level. Patients should fast (1 hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). On non-PK/PD paclitaxel administration days, the morning dose of PLX3397 may be administered at home, prior to paclitaxel administration. Dose escalation will occur in increments of ≤50%. All patients at a given dose level will be followed on treatment for at least 4 weeks before accrual to the next cohort can begin. There will be no intra-patient dose escalation permitted. PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 **only if a patient experiences a DLT.** PLX3397 interruptions during Cycle 1 are also permitted for Grade 3 vomiting that persists despite optimal supportive care. If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be permitted at the discretion of the Investigator and in consultation with the Medical Monitor. After C1D28, dose reductions or interruptions for adverse events (AEs) may take place at any time. **Part 2:** This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (RP2D-treated patients from **Part 1** and **Part 2**). Each treatment cycle will be 28 days. Dosing of PLX3397 will commence at the RP2D. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). There will be no intra-patient dose escalation permitted. PLX3397 dose reductions or interruptions for AEs may take place at any time. **Part 3:** The candidate population will be patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. Patients will be sequentially assigned to one of three Cycle 1 (28-day) lead-in treatment arms: 1) PLX3397 600 mg BID using a continuous dosing regimen 2) Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes 3) PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with PLX3397. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). There will be no intra-patient dose escalation permitted. PLX3397 dose reductions or interruptions for AEs may take place at any time. **Part 1, Part 2, and Part 3:** Patients will receive study treatment as long as it is well tolerated and both the Investigator and Sponsor agree that the patient is clinically benefitting. Reasons for study discontinuation include, but are not limited to, unacceptable toxicity, disease progression, voluntary withdrawal of consent, investigator discretion, and death. After providing informed consent, patients will undergo screening for eligibility to participate

	in the study. Screening will start within 28 days prior to the first study treatment dose. The physical exam and laboratory values should be obtained within 14 days prior to C1D1. Evaluations performed as part of standard-of-care and prior to informed consent may be used if they occur within the protocol-specified timeframe. All female patients of child-bearing potential must have a negative urine pregnancy test within 14 days prior to C1D1. A medical history, including concomitant medications and prior cancer treatment, will be obtained at Screening. A review of new and ongoing concomitant medications will be obtained at each study visit. A standard 12-lead electrocardiogram (ECG), including QTcF, will be performed for each patient at Screening, C1D15, and End of Study. A trans-thoracic echocardiogram (TTE) or multi-gated acquisition (MUGA) scan will be performed for each patient at Screening. Imaging for tumor status will be performed at Screening, and every 8 weeks or as clinically indicated, throughout study participation. A complete physical examination, including height and weight, will be performed for each patient at Screening. A symptom-directed physical exam will be completed on Day 1 (or within 24 hours prior) of each cycle, and at End of Study. Clinical laboratory assessments (hematology and chemistry) will be performed according to the following schedule: • A CBC with platelets must be performed prior to each paclitaxel administration. • Full metabolic panel, including liver transaminases and creatinine, must be performed on Days 1, 8, 15 and 22 (±2 days) of Cycle 1 and on Day 1 for all subsequent cycles. Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) are required at Screening, C1D1, C1D15, Day 1 of all subsequent cycles, and End of Study. Body weight will be measured on the first day of each cycle. The patient's weight must be evaluated on Day 1 of each cycle. The paclitaxel dose must be recalculated if the patient's weight has changed by more than 10% from baseline. Patients will be monitored throughout the study for AEs and compliance with study drug administration. **Part 1:** Blood samples for PLX3397 PK analysis will be obtained pre-PLX3397 and paclitaxel dosing on C1D1, pre-PLX3397 and paclitaxel dosing on C1D15, and 2 and 4 hours post-PLX3397 and paclitaxel dosing on C1D15. **Part 3:** Cancer tissue [2-3 core biopsies of target (≥2 cm diameter) or non-target lesions] for biomarkers will be obtained during Screening after CT imaging and all other screening tests and procedures have been completed and at Cycle 1 Day 28 ± 7 days (Cycle 1 Day 21 to Cycle 1 Day 35). If the second biopsy in Cycle 1 is delayed beyond Day 28, patients will have a Cycle 1 Day 28 visit, during which procedures will be the same as the Cycle 1 Day 22 visit. Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with daily PLX3397 600 mg BID and weekly paclitaxel. Cycle 2 and all subsequent cycles will be 28-day cycles. A blood sample for plasma PK and biomarkers will be obtained pre-PLX3397 and paclitaxel dosing on Cycle 1Day 1, Cycle 1Day 15 and on Day 1 of all subsequent cycles, and End-of-Study Visit. Patients will have efficacy assessments every 8 weeks to determine objective response (CR + PR), clinical benefit (CR + PR + SD), progression-free survival (PFS), and time to next treatment (after last study treatment). CA-125 sampling requirements: 2 pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of C1D1; subsequent samples on the first

	day of each cycle starting with Cycle 2Day 1 and End-of-Study Visit. **Part 1, Part 2, and Part 3:** Pharmacodynamic (PD) markers including serum CSF-1 will be obtained at pre-dose on Day 1 of each cycle as outlined in the Trial Flow Chart. A whole blood sample for circulating CD14/CD16 positive monocyte analysis will also be obtained pre-dose on C1D1 and C1D15.
Key Patient Selection Criteria	Inclusion Criteria 1. Patients in a. **Part 1:** an advanced, incurable solid tumor a. **Part 2:** an advanced, incurable solid tumor for whom a taxane would be considered a reasonable chemotherapy option. b. **Part 3:** advanced, metastatic or non-resectable epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with: i. platinum-resistant cancer, defined as disease that responded to a platinum-containing chemotherapy regimen, but demonstrated recurrence within six months following the completion of that platinum-containing regimen, OR ii. platinum-refractory cancer, defined as disease failed to achieve at least a partial response to a platinum-containing regimen (i.e., stable disease or actual disease progression), AND iii. have not been treated with a taxane within 6 months of C1D1, AND iv. have not been treated with weekly paclitaxel after first-line treatment in which weekly paclitaxel plus a platinum is permitted. 2. **Part 3:** Patients must have target (≥2 cm diameter) or non-target lesion cancer that is accessible for 2-3 core biopsies during Screening after CT imaging and all other screening tests and procedures have been completed and during the period from Cycle 1 Day 21 to Cycle 1 Day 35. 3. Patients with stable brain metastases are eligible for this trial. However, patients must not have required steroid treatment for their brain metastases within 30 days of Screening. 4. Bone-directed therapy (e.g., bisphosphonates or denosumab) is permitted. However, patients should not have started bone-directed therapy within 2 weeks of C1D1, and new bone-directed therapy should not be initiated during the first 4 weeks of study (i.e., Cycle 1). 5. Washout from any prior investigational therapy of at least five times the $T_{1/2}$ prior to C1D1. 6. Washout from any prior biologic or targeted therapy at least 4 weeks or five times the $T_{1/2}$ (whichever is shorter) prior to C1D1. 7. Washout from prior chemotherapy of at least 2 weeks or 1 elimination half-life, whichever is longer, prior to C1D1. 8. Washout from prior hormonal therapy of at least 2 weeks, prior to C1D1. 9. Washout of at least 2 weeks from the most recent radiation treatment prior to C1D1. 10. Resolution of all prior treatment-related toxicities to Grade 1 or less, except for

	Grade 2 fatigue or alopecia prior to C1D1 11. Age eighteen years or older. 12. ECOG performance status 0–2, inclusive. 13. Anticipated life expectancy of at least 12 weeks. 14. Adequate bone marrow reserve: ANC ≥1500/mm^3, platelets ≥100,000/mm^3. 15. Adequate renal function: serum creatinine <1.5 x ULN or calculated CrCl >60 mL/min using Cockcroft-Gault formula GFR = [(140-age)•(weight in kg)•(0.85 if female)]/(72•Cr). 16. Adequate hepatic function: AST and ALT <2.5 x ULN; Total and Direct Bilirubin <1.5 x ULN. However, in the presence of liver metastases, AST and ALT must be <5 x ULN. 17. Cardiac ejection fraction ≥50%, and QTcF <450 ms (males) or <470 ms (females) on ECG at Baseline. Fridericia's Formula: QTcF = (QT)/RR$^{0.33}$ 18. Able to swallow capsules and maintain adequate hydration. 19. Ability to give written informed consent and willing to comply with the requirements of the protocol; and for **Part 3,** able to give written informed consent for 2 cancer biopsy procedures. 20. Women of child-bearing potential must agree to use an effective method of birth control during treatment and for three months after receiving their last dose of study drug. Sexually active men must also agree to use an acceptable method of birth control while on study drug and for at least 3 months after last dose (see Attachment 4).
Key Patient Selection Criteria Cont'd	Exclusion Criteria 1. Presence of a secondary active malignancy • Patients with a non-melanomatous, in situ malignancy or disease that is completely resectable with surgery may be considered after discussion with the Medical Monitor • Patients with a completely treated prior malignancy with no evidence of disease for ≥3 years are eligible 2. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant small bowel resection that would preclude adequate absorption of PLX3397. 3. Ongoing treatment with any other investigational therapy. 4. Prior anaphylactic or severe hypersensitivity reaction to paclitaxel or Cremaphor-containing agent. 5. Persistent Grade 2 fatigue at Baseline. 6. Severe, concurrent illness including congestive heart failure, significant cardiac disease and uncontrolled hypertension, that would likely prevent the patient from being able to comply with the study protocol. 7. Active untreated infection 8. Known chronic active hepatitis B or C or HIV infection 9. The presence of a medical or psychiatric condition that, in the opinion of the Principal Investigator, makes the patient inappropriate for inclusion in this study
Duration of Study	The duration of the study will depend on the recruitment rate and the duration of treatment for those patients enrolled.

Dose Limiting Toxicities	**Part 1:** Patients must receive at least 21 days of PLX3397 AND at least 3 doses of paclitaxel during the first 28 day cycle in order to be considered evaluable for DLT, unless doses are missed due to a DLT. <u>Hematologic DLTs</u> • Grade 4 neutropenia lasting for ≥7 days in duration • Grade 4 thrombocytopenia (platelets ≤25.0/μL) • Grade 3 thrombocytopenia associated with bleeding <u>Other DLTs</u> • Any CTCAEv4 Grade ≥3 other toxicity, **unless the event is clearly unrelated** to treatment with PLX3397 in combination with weekly standard fixed dosing of paclitaxel EXCEPT the following: o Allergic reaction to paclitaxel o Grade ≥3 nausea, vomiting, or diarrhea that resolves to Grade ≤2 within 48 hours, with or without medical intervention or prophylaxis o Grade 3 fatigue that resolves to ≤Grade 2 within 14 days o Grade ≥3 hyperglycemia o Transient (<14 days) increase in LFTs of ≤one Grade in severity compared to baseline levels in patients with baseline liver metastases o Grade 3 peripheral neuropathy in patients with baseline ≥Grade 1 peripheral neuropathy or a history of chemotherapy-associated peripheral neuropathy o Grade 3 myalgia or arthralgia in patients with baseline ≥Grade 1 myalgia or arthralgia o Grade 3 rash for which symptoms are easily managed with supportive care and there is no evidence of superinfection or limitation of self-care ADLs
Dosage and Regimen	PLX3397 (200 mg capsules) will be administered orally, using a dosing regimen of twice daily. Patients should fast (1 hour) before and after PLX3397 administration on an empty stomach (see Section 14.1.1 for details). The BID regimen is preferred to reduce capsule load per dose and minimize intra-day drug level fluctuations. On non-PK or non-blood biomarker dosing days, PLX3397 may be administered at home, prior to the clinic visit for paclitaxel administration. **Part 1:** At least 3 of 4 planned paclitaxel doses must be administered in the DLT period (i.e., Cycle 1). On subsequent cycles, 1 paclitaxel dose may be skipped per Cycle per Investigator discretion and/or patient preference. **Part 2:** Patients will be treated with PLX3397 RP2D (600 mg BID) using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. One paclitaxel dose may be omitted per cycle by physician discretion. **Part 3:** Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms: • PLX3397 600 mg BID using a continuous dosing regimen. • Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. • PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes.

	Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with PLX3397. **Part 1, Part 2, and Part 3:** In order to initiate each weekly paclitaxel treatment, patients must have an ANC ≥1000/mm^3 and platelets ≥75,000/mm^3. A paclitaxel premedication regimen, consisting of a corticosteroid, an H2 antagonist and diphenhydramine, is recommended in order to reduce the risk of anaphylaxis.
Safety and Tolerability Assessments	Physical examinations, vital signs, AEs, hematology, serum chemistry, and ECGs will be used to assess safety and tolerability. **Part 3:** AE and serious adverse event (SAE) reporting will commence when the 2-3 core biopsies are obtained during Screening**.**
Stopping Rules	**Part 1:** If ≥2 of 6 patients in Dose Level -1 either experience a DLT or are unable to receive the requisite PLX3397 and paclitaxel doses in the first 28 days due to treatment-related adverse events, the combination will be considered too toxic and the study will be discontinued. **Part 2:** After ~50% of the planned approximately 30 patients (RP2D-treated patients from **Part 1** and **Part 2**) have completed at least 2 treatment Cycles, an overall interim safety summary will be reviewed by the Medical Monitor and Principal Investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not warrant continued enrollment, the study will be discontinued. **Part 3:** After ~50% of the approximately planned 30 patients have completed at least 2 treatment Cycles, an overall interim safety summary will be reviewed by the Medical Monitor and Principal Investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not warrant continued enrolment, the study will be discontinued.
PK Parameters	**Part 1 and Part 3:** PLX3397 levels will be evaluated at steady state (C1D15).
PD Parameters	**Part 1, Part 2, and Part 3:** Exploratory biomarkers for evaluating anti-tumor activity, inflammation and energy metabolism may be measured. Biomarkers will include, but are not limited to, CSF-1. **Part 3:** Cancer tissue biomarkers will include: • Immunohistochemistry for CD68, CD8, PD-L1, and additional markers of macrophage and T-cell presence and function • RNA expression analysis for an exploratory panel of tumor microenvironment markers • Staining of cells of the tumor microenvironment. Panels of IHC markers specific for macrophages, T-cells, and other immune and inflammatory cells will be employed, for semi-quantitative changes in cell number, location within the tumor, and degree of activation.

	Blood biomarkers will include: • CA-125 • Plasma CSF-1 and additional markers of treatment effect • Whole blood CD14/CD16 monocyte subset by flow cytometry (FACS) analysis • Whole blood myeloid-derived suppressor cell (MDSC) by FACS analysis

Trial Flow Chart (Part 1 and Part 2)

	Screening		Cycle 1				Cycle 2+					
STUDY DAY►	**Day -28 to -1**	**Day -14 to -1**	**Day 1 (Baseline) (-2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**	**Day 1 (±2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**	**Other Schedules**	**End of Study**
EVENT▼												
Informed Consent	X											
Medical History	X											
Prior Cancer Treatment	X											
Height	X											
Weight	X		X				X					X
Vital Signs[10]	X		X				X					X
Physical Exam[1]		X	X				X					X
12-lead ECG[11]	X				X							X
Echocardiogram or MUGA	X											
Chemistry[14]		X	X	X	X	X	X					X
Hematology[12]		X	X	X	X	X	X	X	X	X		X
Urine Pregnancy Test[13]		X										X
Imaging	X										Every 8 weeks or as indicated	X[16]
Concomitant Medications	X		X	X	X	X	X	X	X	X		X
ECOG Performance Status Assessment	X		X				X					X

	Screening		Cycle 1				Cycle 2+					
STUDY DAY►	**Day -28 to -1**	**Day -14 to -1**	**Day 1 (Baseline) (-2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**	**Day 1 (±2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**	**Other Schedules**	**End of Study**
EVENT▼												
PLX3397 Administration[2]			X	X ———						X	Administer Daily	
PLX3397 Compliance			X	X	X	X	X	X	X	X		X
Paclitaxel Premedications[3]			X	X	X	X	X	X	X	X		
Paclitaxel Administration[4, 6]			X	X	X	X	X[5]	X[5]	X[5]	X[5]		
Plasma for PK (Part 1 only)			X[7]		X[8]		X[7]					
Plasma for PD biomarkers			X[15]				X[15]					
Whole Blood Sample for CD14/CD16 analysis			X		X							
Adverse Events[9]			X	X	X	X	X	X	X	X		X

EXPLANATION OF SUPERSCRIPTS:

1. Full physical exam at Screening only, and symptom-directed physical exam subsequently.
2. On clinic visit days, PLX3397 may be taken at any time prior to paclitaxel administration. The a m. dose of PLX3397 may be taken at home, prior to the clinic visit on all clinic visit days ***EXCEPT*** on C1D1 (Baseline), C1D15, and C2+D1. On those study days, the morning dose of PLX3397 will be administered in the clinic after obtaining a pre-dose blood sample for PK or PD biomarker analysis. PLX3397 should be administered at approximately the same time(s) each day, ±2 hours. Patients should fast for at least 1 hour before and after PLX3397 administration (see Section 14.1.1 for details)
3. Paclitaxel premedications are recommended, but not required. The premedication regimen includes a corticosteroid, H_2 antagonist and diphenhydramine.
4. Investigators should follow standard institutional guidelines.
5. Paclitaxel doses are administered on these scheduled days ±48 hours.
6. One dose of paclitaxel may be skipped every Cycle per Investigator discretion and patient preference *after Cycle 1*.

7. **Part 1 only:** Plasma samples for PK on C1D1 and the first day of all subsequent cycles (i.e., C2+D1) are obtained prior to the first dose of PLX3397.
8. **Part 1 only:** Plasma sample for PK on C1D15 will occur pre-PLX3397 administration and at 2 and 4 hours post PLX3397 dosing.
9. Monitored throughout the study via safety assessments, observation, and participant reporting.
10. Should be taken 3–5 minutes after sitting. Includes pulse, respiratory rate, temperature and blood pressure
11. Should be completed after the patients have been in a supine position for at least 5 minutes.
12. Hematology evaluation must include CBC with differential (see Attachment 1). ANC must be $\geq 1000/mm^3$ and Platelets must be $\geq 75{,}000/mm^3$ for paclitaxel administration.
13. Required for all female patients of child-bearing potential.
14. Chemistry evaluation must include a full metabolic panel (see Attachment 1)
15. **Part 1 and Part 2:** Samples for PD biomarkers to be obtained prior to PLX3397 administration.
16. End of Study imaging should be obtained for patients who go off study for reasons other than radiographic disease progression

Trial Flow Chart (Part 3)

	Screening		Cycle 1 Lead-in Phase (28-35 day cycle)				Cycle 2+ (28 day cycles)				Other Schedules	End of Study
STUDY DAY►	**Day -28 to -1**	**Day -14 to -1**	**Day 1 (Baseline) (-2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**	**Day 1 (±2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**		
EVENT▼												
Informed Consent	X											
Assignment of Lead-in Treatment Arm	X											
Medical History	X											
Prior Cancer Treatment	X											
Height	X											
Weight	X		X				X					X
Vital Signs[1]	X		X				X					X
Physical Exam[2]		X	X				X					X
ECOG PS	X		X				X					X
12-lead ECG[3]	X				X							X
Echocardiogram or MUGA	X											
Chemistry[4]		X	X	X	X	X	X	X[20]	X[20]	X[20]		X
Hematology[5]		X	X	X	X	X	X	X	X	X		X
Urine Pregnancy Test[6]		X										X
Imaging	X										Every 8 weeks or as indicated	X[19]
Concomitant Medications	X		X	X	X	X	X	X	X	X		X

	Screening		Cycle 1 Lead-in Phase (28-35 day cycle)				Cycle 2+ (28 day cycles)					
STUDY DAY►	**Day -28 to -1**	**Day -14 to -1**	**Day 1 (Baseline) (-2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**	**Day 1 (±2 Days)**	**Day 8 (±2 Days)**	**Day 15 (±2 Days)**	**Day 22 (±2 Days)**	**Other Schedules**	**End of Study**
EVENT▼												
PLX3397 Administration[7]			X[8,9] ———			X[8,9]	X ———			X	Administer Daily	
PLX3397 Compliance			X[8,9]	X[8,9]	X[8,9]	X[8,9]	X	X	X	X		X
Paclitaxel Administration[11]			X[9,10]	X[9,10]	X[9,10]	X[9,10]	X[12,13]	X[12,13]	X[12,13]	X[12,13]		
Plasma for PK & PD Biomarkers[14]			X		X		X					X
Cancer Tissue Biomarkers[15]	X						X					
CA-125	X[16]		X[16]				X[16]					X[16]
Whole Blood for CD14/CD16 analysis[14]			X		X							
Whole Blood for MDSC analysis[14]			X		X							
Adverse Events[17]	X[18]		X	X	X	X	X	X	X	X		X

EXPLANATION OF SUPERSCRIPTS:

1. Vital signs should be taken 3–5 minutes after sitting. Includes pulse, respiratory rate, temperature and blood pressure.
2. Full physical exam at Screening only, and symptom-directed physical exam subsequently.
3. ECGs should be completed after the patients have been in a supine position for at least 5 minutes.
4. Chemistry evaluation must include a full metabolic panel (see Attachment 1).
5. Hematology evaluation must include CBC with differential (see Attachment 1). ANC must be ≥1000/mm^3 and Platelets must be ≥75,000/mm^3 for paclitaxel administration.
6. Required for all female patients of child-bearing potential.
7. On clinic visit days, PLX3397 may be taken at any time prior to paclitaxel administration. The AM dose of PLX3397 may be taken at home prior to the clinic visit on all clinic visit days ***EXCEPT*** on C1D1 (Baseline) and C2+D1. On those study days, the morning dose of PLX3397 will be administered in

the clinic after obtaining a pre-dose blood sample for PD biomarker analysis. PLX3397 should be administered at approximately the same time(s) each day, ±2 hours. Patients should fast for at least 1 hour before and 1 hour after PLX3397 administration (see Section 14.1.1 for details).

8. This assessment schedule is applicable for all patients randomized to the **Lead-In PLX3397 Alone Arm**.
9. This assessment schedule is applicable for all patients randomized to the **Lead-in PLX3397 and Paclitaxel Arm**.
10. This assessment schedule is applicable for all patients randomized to the **Lead-in Paclitaxel Alone Arm**.
11. Investigators should follow standard institutional guidelines for paclitaxel administration. Paclitaxel premedications are recommended, but not required. The premedication regimen includes a corticosteroid, H_2 antagonist and diphenhydramine.
12. Paclitaxel doses are administered on these scheduled days ±48 hours.
13. One dose of paclitaxel may be skipped every Cycle per Investigator discretion and patient preference *after Cycle 1*.
14. Blood for plasma PK and PD biomarkers will be obtained prior to treatment on Cycle 1 Day 1, Cycle 1 Day 15 and on Day 1 of all subsequent cycles. Plasma sample for PK on C1D15 will occur pre PLX3397 administration and at 2, 4, and 6 hours post PLX3397 dosing. Separate whole blood samples for CD14/CD16 and MDSC analyses will be obtained prior to treatment on Cycle 1 Day 1 and Cycle 1 Day 15.
15. Paired tissue biopsies [2-3 core biopsies of target (≥2 cm diameter) or non-target lesions] will be obtained at Screening after CT imaging and all other screening tests and procedures have been completed and during the period from Cycle 1 Day 21 to Cycle 1 Day 35. If the second biopsy in Cycle 1 is delayed beyond Day 28, patients will have a Cycle 1 Day 28 visit for paclitaxel administration (performed weekly), during which study procedures will be the same as the Cycle 1 Day 22 visit.
16. CA-125 sampling requirements: two pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of C1D1; subsequent samples on the first day of each cycle starting with Cycle 2 Day 1 and End-of-Study Visit.
17. Monitored throughout the study via safety assessments, observation, and participant reporting.
18. Serious and non-serious adverse event reporting will commence when the 2-3 core biopsies are obtained during Screening**.**
19. End of Study imaging should be obtained for patients who go off-study for reasons other than radiographic disease progression.
20. **Cycle 2 only:** serum chemistry required prior to paclitaxel administration for **Part 3 – all arms**.
    Cycle 3 only: serum chemistry only required for **Part 3 Lead-in Paclitaxel Alone Arm**.

7.0 INTRODUCTION

7.1 Background

For women in United States, breast cancer is the most common malignancy, the second most common cause of cancer-related death and the main cause of death for women between the ages of 40–59 years (Jemal 2010). Approximately 10% of women diagnosed with breast cancer have locally advanced (i.e., Stage III) disease, accounting for approximately 23,000 new cases in the United States in 2011 (Newman 2009; American Cancer Society 2011).

Microtubule function is vital to cell survival and plays an important role in proliferation and motility, maintenance of cell shape and protein trafficking. Several agents affecting microtubule dynamics are active anti-tumor agents and induce polymerization, or cause non-functional tubulin aggregates blocking cell division by interfering with mitotic spindle function, consequently resulting in cell cycle arrest and cell death (Horwitz 1994). Microtubule stabilizers are considered one of the most effective classes of agents available for treating early and late stage BC, and paclitaxel (PTX), which exerts its anti-tumor activity through microtubule stabilization, is one of the most widely used agents in this class. Weekly paclitaxel has been shown to be superior to 3-weekly paclitaxel in the treatment of MBC in both response rate (RR) and time-to-progression (TTP) (Seidman 2008).

Macrophages and Breast Cancer

Macrophages are the most abundant innate immune cell type present within breast cancer, where they regulate angiogenic processes via production of pro-angiogenic factors including vascular endothelial growth factor (VEGF) and proteases (Lin 2007). In breast cancer patients, cytotoxic therapies prominently increase the presence of macrophages in residual tumors and alter the tumor immune microenvironment (Ruffell 2012). In a transgenic mouse model of mammary adenocarcinoma development (e.g., MMTV-PyMT mice)[34], increased macrophage infiltration in premalignant tissue occurs immediately before activation of angiogenesis and onset of malignancy [35, 36]. Colony stimulating factor-1 (CSF-1) is broadly expressed by mammary tumor cells, and its expression correlates with extent of macrophage infiltration (Guy 1992). MMTV-PyMT mice carrying the Csf1op/op mutation exhibit 95% decreased infiltration of macrophages in tumors, inhibited angiogenesis, significantly delayed tumor progression and diminished pulmonary metastasis (Lin 2001).

In breast cancer, macrophages are regulated in part by CSF-1, mediated by Fms (i.e., the CSF-1 receptor) (Tang 1992). Paracrine interactions between macrophages and microvascular endothelial cells (MECs) form positive feed-forward loops involving macrophage-expressed EGF. Together with CSF-1 expressed by neoplastic cells, these paracrine interactions regulate carcinoma cell chemotaxis along collagen fibers towards blood vessels directed by perivascular macrophages (Condeelis 2006; Condeelis 2003). Based on these findings, it seems reasonable to postulate that blockade of cellular and/or molecular programs enhancing macrophage recruitment

in breast cancer may represent tractable targets for anti-cancer therapy. Indeed, blockade of CSF-1 or Fms results in decreased macrophage presence in tissues and in experimental tumors, correlates with diminished angiogenesis, reduced tumor growth metastasis in some models (Lin 2001; Nowicki 1996; Conway 2005; Manthey 2009; Priceman 2010; Qian 2009).

CSF-1 Receptor Inhibition in Ovarian Cancer

In human epithelial ovarian cancer, CSF-1 and/or Fms expression has been observed in the large majority of cases, with 75% of primary tumors and 69% of the metastases expressing CSF-1, and 92% of primary tumors and 83% of metastases expressing Fms (Kacinski 1991; Chambers 1997; Toy 2001). At the time of diagnosis in epithelial ovarian cancer patients, elevated levels of both serum and ascitic fluid CSF-1 are associated with a poor outcome (Price 1993, Scholl 1994). During the course of the disease, elevated levels of serum CSF-1 can herald disease recurrence or progression (Kacinski 1989). Elevated CSF-1 levels as part of a panel of markers, including CA125, has recently been shown to help improve early detection of ovarian cancer (Skates 2004; Zhang 2007). This strong association with disease detection and prognosis suggests an etiological role for Fms/CSF-1 in ovarian cancer initiation and neoplastic progression.

Based on the findings discussed above, it seems reasonable to postulate that blockade of cellular and/or molecular programs enhancing macrophage recruitment in epithelial ovarian cancer may result in decreased macrophage presence in epithelial ovarian tumors.

PLX3397 as a Macrophage-Targeted Tumor Sensitizer

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

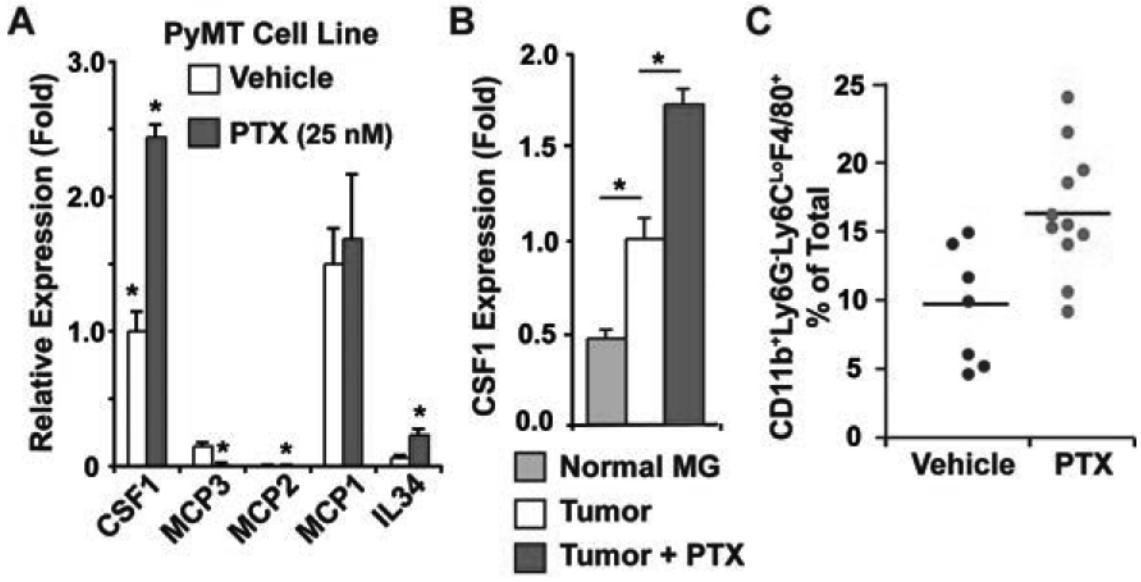
An important role for tumor-infiltrating macrophages in tumor progression has pointed to Fms as a key target in multiple tumor types (Ruffell 2015). The pro-tumorigenic role of CSF1 and Fms is supported by a wealth of studies demonstrating that CSF-1 levels predict a poor outcome in a variety of oncology indications, including breast, ovarian, non-small cell lung, and colorectal cancers.

Cytotoxics Induce Expression of Macrophage/Monocyte Chemoattractants

In vitro studies of MECs from murine mammary and human breast tumors demonstrate that levels of macrophage and immature myeloid suppressor cell (IMC) chemoattractant mRNA, including CSF-1, CCL8/MCP2 and IL34, increase following exposure to paclitaxel, cisplatin and radiation.

To reveal the molecular mediators involved in CTX-associated macrophage recruitment, we evaluated MECs from murine mammary and human breast tumors in vitro for mRNA expression of monocyte/macrophage cytokines/chemokines following exposure to PTX, cisplatin or radiation therapy, and found increased expression of important macrophage/IMC chemoattractant mRNAs, including CSF1, CCL8/MCP2 and IL34 (Figure 1A) shows analysis of PyMT-derived carcinoma cells treated with PTX in vitro). Analysis of *CSF1* mRNA expression in vivo revealed that mammary tumors of MMTV-PyMT mice had a 2-fold higher expression of CSF1 mRNA following PTX exposure (Figure 1B) that correlated with increased density of macrophage in tumor stroma (Figure 1C).

Figure 1: In Vitro Paclitaxel Exposure Results in Increased CSF-1 and Macrophage Density in Mammary Tumor Stroma



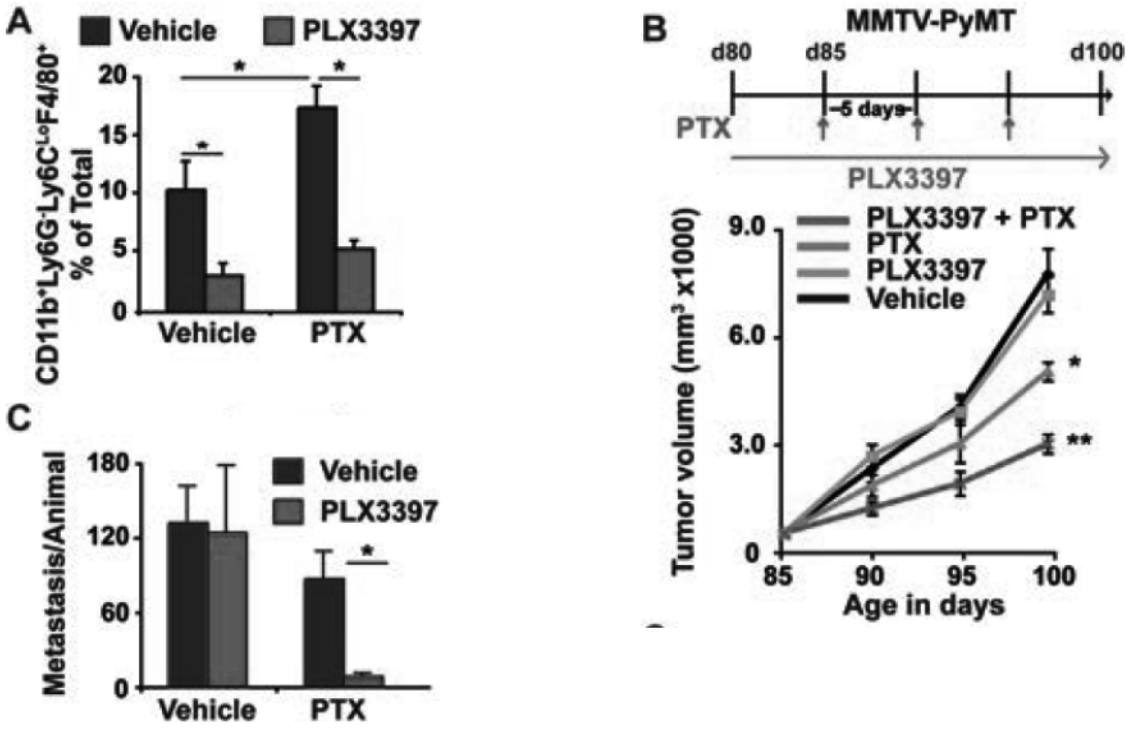
A) QRT-PCR analyses of CSF1, MCP1, MCP2, MCP3 and IL34 expression in PyMT-carcinoma cells treated with PTX for 24 hours; B) PTX-induced CSF1 mRNA expression; and C) Macrophage density in mammary tumors of MMTV-PyMT mice following PTX treatment.

(*) $p < 0.05$.

PLX3397 blocks paclitaxel-induced macrophage recruitment to mammary tumors and improves tumor chemosensitivity.

In vivo studies in late-stage MMTV-PyMT mice treated with paclitaxel ± PLX3397 (see Figure 2) showed that the combination was associated with 1) reduced macrophage infiltration of tumor tissue, 2) statistically significant reduction in tumor growth and 3) statistically significant reduction in the occurrence of pulmonary metastases compared to paclitaxel alone.

Figure 2: PLX3397 + Paclitaxel



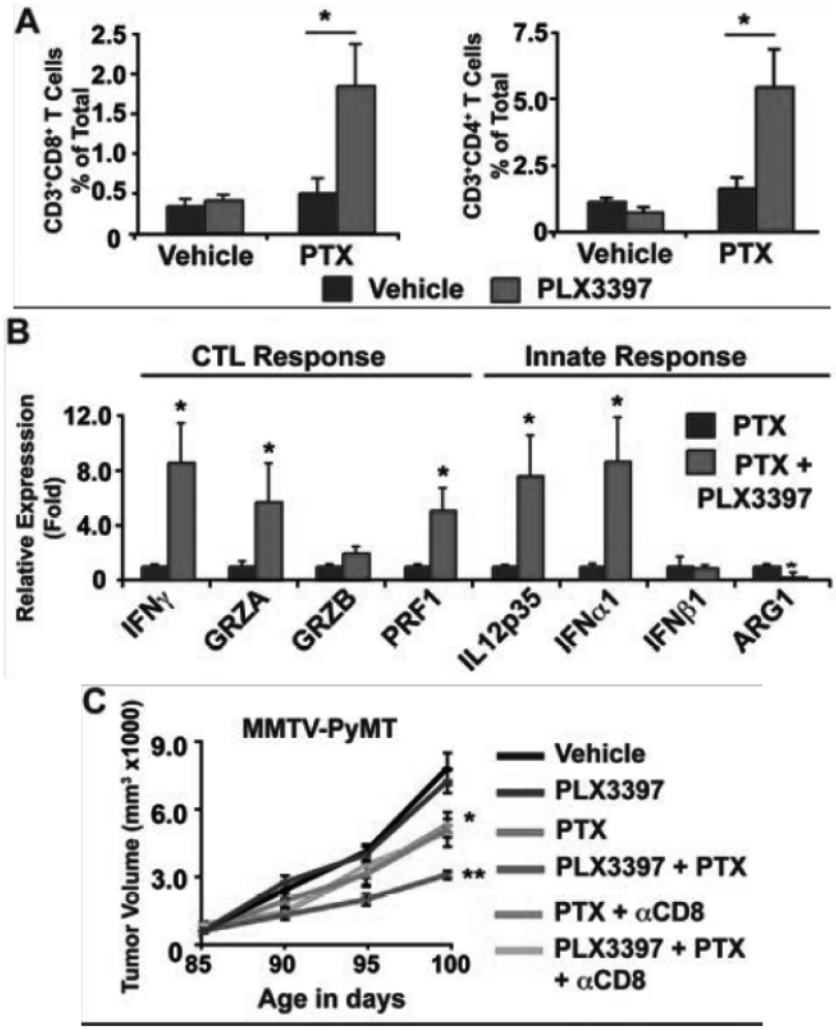
A) PLX3397 blocks macrophage-recruitment in MMTV-PyMT mammary tumors; B) 85-day-old MMTV-PyMT mice were treated with PTX +/- PLX3397 and tumor burden per animal assessed every 5 days until endpoint; and C) Quantitation of metastatic foci/lung section/mouse from 100-day-old MMTV-PyMT mice treated with PTX, and/or PLX3397.

(*) $p<0.05$, (**) $p<0.01$.

Combination PLX3397 + paclitaxel treatment is associated with increased anti-tumor immunity.

Tumors from PLX3397/paclitaxel-treated MMTV-PyMT mice revealed increased % of CD4+, CD8+ T cells and dendritic cells (DCs) (data not shown), correlating with significantly ($p<0.05$) increased expression of cytotoxic effector molecules (interferon (IFN)-γ, granzyme A (GRZA), granzyme B (GRZB), perforin-1 (PRF1), and "Type-1" DC effectors molecules IL12p35 and interferon (IFNα) (DeNardo 2011), and decreased expression of immunosuppressive ARG1, thus indicating an overall reprogramming of the immune microenvironment (Figure 3).

Figure 3: Immunomodulatory Effects in Tumors of PLX3397/PTX-Treated MMTV-PyMT Mice



A) Increased CD4 and CD8 T cells in tumors of PLX3397/PTX treated MMTV-PyMT mice; B) Mean fold change in cytokine mRNA expression of PyMT tumors from mice treated with PTX alone or in combination with PLX3397; and C) 85-day-old MMTV-PyMT mice were treated with PTX and/or PLX3397 and anti-CD8 IgG. Total tumor burden/animal was assessed every 5 days.

(*) $p<0.05$, (**) $p<0.01$.

7.2 PLX3397 Nonclinical Pharmacodynamics

In brief, biochemical data support Fms, Kit and oncogenic Flt3 as key targets of PLX3397.Consequently, proliferation of cell lines that alternatively depend on CSF-1 or SCF ligands, or are driven by Flt3 that is oncogenically activated by internal tandem duplications (Flt3-ITD), is inhibited by PLX3397 at IC_{50} values well below 1 μM. Furthermore, CSF-1-induced autophosphorylation of Fms and SCF-induced autophosphorylation of Kit are potently inhibited by PLX3397. By contrast, both autophosphorylation and proliferation of cells induced

by addition of Flt3 ligand are only weakly inhibited by PLX3397, suggesting preferential inhibition of the oncogenically-activated Flt3 kinase. Finally, the RANK-L and CSF-1-dependent differentiation of osteoclast precursors is also potently inhibited by PLX3397.These in vitro effects translated to effects in a variety of in vivo models designed to test the effects of PLX3397 on Fms-dependent proliferation, Fms-dependent osteoclast differentiation, and Flt3-ITD dependent tumor growth.

Please refer to the Investigator's Brochure for additional information on Fms and Kit inhibition.

7.2.1 In Vitro Pharmacodynamics

PLX3397 shows significant selectivity for Fms (i.e., CSF-1R), Kit and oncogenically active Flt3 (i.e., Flt3-ITD) versus a panel of over 200 kinases, with IC_{50} values of 17, 12 and 9 nM, respectively (see Table 1).

Table 1: IC_{50} Values of PLX3397 Against Selected Kinases

Kinase	Fms	Kit	Flt3-ITD[a]	Kdr	Lck	Flt1	TrkC
PLX3397	17 nM	12 nM	9 nM	213 nM	860 nM	880 nM	890 nM

[a] Flt3-ITD indicates a kinase domain activated via truncation.

Unactivated (i.e., wild-type) Flt3 has measurable activity that is 15-fold less sensitive to PLX3397. Kdr kinase activity is only modestly affected, and other kinases tested are even less sensitive to PLX3397. While physiologic effects due to the inhibition of Fms and Kit are expected, the selectivity of PLX3397 suggests that minimal off-target effects should be observed. When screened against a broad panel of additional kinases, IC_{50} values were >1 µM for all, with the majority >10 µM.

PLX3397 also demonstrated negligible activity in a standard Novascreen panel. This is a screen for off-target activity against a broad array of 71 targets in 8 families (Neurotransmitter-related, Steroids, Ion Channels, Nitric Oxide, Prostaglandins, Growth Factors, Brain/Gut Peptides, and Enzymes). At a concentration of 10 µM serum-free, all results were within 40% of Baseline, indicating no relevant off-target activity.

Several in vitro experiments have demonstrated that PLX3397 spares the wild-type Flt3 and is selective for the oncogenic Flt3-ITD. BaF3 cells are mouse pre-B cells that depend on interleukin-3 (IL-3) for survival. By engineering BaF3 cells to express BCR-activated Flt3 kinase activity (truncated Flt3 kinase domain), the dependence on IL-3 can be replaced. Consequently, these BCR-Flt3 expressing BaF3 cells are dependent on a truncated Flt3 kinase activity for survival. In vitro, PLX3397 inhibits proliferation of that line with an IC_{50} of 400 nM. Addition of IL-3 to the BaF3-Flt3 cells 'rescues' these cells and shifts the IC_{50} to greater than 10,000 nM, reflecting a robust therapeutic index.

In RS4;11 cells, Flt3 autophosphorylation and proliferation can be induced by Flt3 ligand and this autophosphorylation requires high levels of PLX3397 (1500 nM) for inhibition, suggesting that PLX3397 binds only weakly to unactivated Flt3. On the other hand, kinase activity and proliferation of MV4-11 cells (that express Flt3-ITD) is potently inhibited by PLX3397 with an IC_{50} value of 26 nM.

For additional information regarding PLX3397 in vitro pharmacodynamics and inhibition of Fms and Kit, please refer to the Investigator's Brochure.

7.2.2 In Vivo Pharmacodynamics

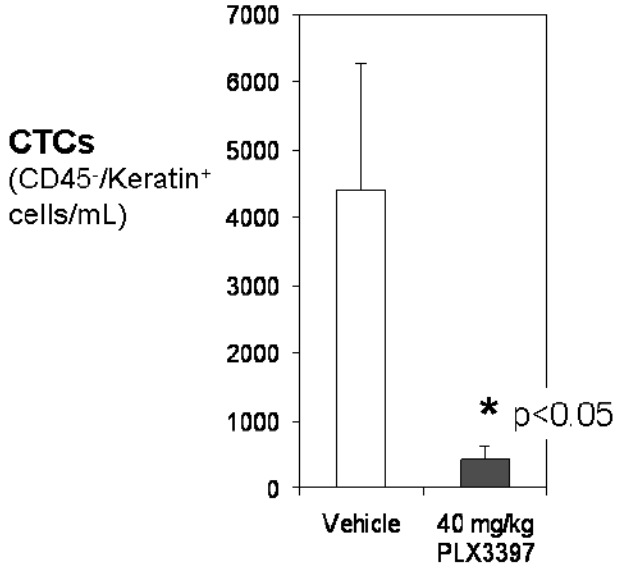
Models of Fms-dependent proliferation and Fms-dependent osteoclast activity can be inhibited by 5–10 mg/kg doses of PLX3397 in vivo. This was demonstrated in a Fms-dependent splenomegaly model, a metastatic breast cancer model, and a murine collagen-induced arthritis model.

BaF3 cells are mouse pre-B cells that depend on interleukin-3 (IL-3) for survival. By engineering BaF3 cells to express BCR-activated Fms kinase activity, the dependence on IL-3 can be replaced. Consequently, these BCR-Fms expressing BaF3 cells are dependent on Fms kinase activity for survival. In vitro, proliferation of these cells can be potently inhibited by PLX3397, with an IC_{50} value of 7 nM. A corresponding BaF3 cell line expressing BCR-Kit is also quite sensitive to PLX3397, with an IC_{50} value of 130 nM.

Injection of the BCR-Fms-expressing BaF3 cells into the tail vein of nude mice results in homing of these cells to the spleen and subsequent cellular proliferation that results in dramatic splenomegaly over the course of 14–18 days. Oral dosing of PLX3397 for the final 8 days of this model results in dose-dependent inhibition of the splenomegaly. The ED-50 of this effect is between 2 and 5 mg/kg. Therefore, we believe that a 5 mg/kg oral dose of PLX3397 in mice corresponds to an efficacious dose. Pharmacokinetic analysis reveals that this 5 mg/kg dose achieves an $AUC_{(0–24)}$ of 99.8 μM•h, and a C_{max} of 13.4 μM. We will use these values to define an efficacious exposure, and this will be used as the denominator in calculations of therapeutic multiples.

In a separate model, mice expressing the polyoma middle T antigen (PyMT) behind a mammary promoter develop breast cancer that metastasizes after several months. During the metastatic process, circulating tumor cells that express PyMT can be measured among circulating blood cells. Since Fms activity is a critical component of extravasation into the blood stream, reduction in the number of these circulating tumor cells can be a measure of anti-Fms activity. Within 24 hours of a single oral dose of 40 mg/kg PLX3397, a 10-fold decrease in these circulating tumor cells can be determined (see Figure 4).

Figure 4: PLX3397-Induced Reduction of Circulating Tumor Cells in PyMT Mouse Model of Breast Cancer



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

7.3 PLX3397 Nonclinical Metabolism and Pharmacokinetics

Please refer to the PLX3397 Investigator's Brochure for updated information and detailed description of the nonclinical metabolism and PK.

PLX3397 has low aqueous solubility and modest permeability. It is not a substrate or inhibitor of Pgp. Several studies in four species (mouse, rat, dog, and monkey) evaluated formulations to optimize absorption and systemic exposure following oral administration. PLX3397 was absorbed within two to three hours following oral administration. In several studies, plasma exposure (based on AUC values) was greater in females (up to 34% in rats). Elimination half-lives ranged from 2 to 5 hours in these four species. A study conducted in cynomolgus monkeys showed that food does not inhibit or delay absorption of PLX3397 following oral (gavage) administration.

The extent to which PLX3397 binds to the plasma proteins was evaluated in vitro using a Rapid Equilibrium Dialysis inverted method. PLX3397 is strongly protein bound in plasma for all four species tested (mouse, rat, dog, and human). With regards to potential species differences, the binding in mouse, dog and human plasma at 75 µM was approximately equal (99.8%, 99.7%, and 99.8% respectively) while rat protein binding was marginally lower (98.3%).

Two experiments evaluated the partitioning of PLX3397 between blood and brain, based on measurements of test article in brain tissue, cerebrospinal fluid and plasma. In one study, appreciable amounts of PLX3397 were recovered in whole blood (vs. plasma), suggesting that PLX3397 associates with cellular elements of blood. In experiments that quantified PLX3397 concentration in brain tissue and cerebrospinal fluid 4 and 6 hours following oral administration in rats, the brain: plasma ratio averaged 0.41 and 0.36, respectively–values close to that of antipyrene, a positive control (0.50 and 0.54). The ratios of CSF: plasma at these time points for PLX3397, however, were lower (0.026 and 0.014) than those for antipyrene (1.06 and 0.92).

A series of in vitro studies examined the metabolic stability of PLX3397 using either liver S9 fraction or intact hepatocytes from several species, including rats and dogs, the two species used in toxicology studies, as well as humans. Studies with intact hepatocytes revealed that PLX3397 was very slowly metabolized in all three species, especially human liver cells. Although the exact molecular species were not identified, in the presence of human hepatocytes, several molecular species corresponding to glucuronide conjugates were detected, with minimal evidence of breakdown. These data, along with the high protein binding, suggests that the clearance of PLX3397 from human plasma may be slow. Another study was conducted to evaluate the CYP450 phenotypes of PLX3397 metabolism in vitro. Of the five major CYP isoforms, 3A4 (BFC) may be involved in Phase I metabolism of PLX3397, with possibly CYP1A2 playing a minor role.

PLX3397 does not appear to inhibit CYP drug-metabolizing enzymes to an important extent. Studies using human liver microsomes yielded enzyme inhibitory constant (K_i) values exceeding 30 μM for CYP1A2 and 3A4 (testosterone substrate), $\geq$12 μM for 3A4 (midazolam substrate), 2D6 and 2C9.A K_i value <10 μM was obtained for only one CYP isozyme: 2C19 (K_i = 8.4 μM). It is worth noting that the latter experiment was conducted in the absence of human serum albumin (HSA). When PLX3397 was evaluated for its ability to inhibit the major human CYP isozymes in the presence of 10 μM HSA, IC_{50} values greater than 30 μM were uniformly obtained. In another series of experiments, PLX3397 was demonstrated not to induce the expression of genes that encode CYP enzymes and several other proteins involved in metabolism and transport.

In aggregate, an extensive series of non-clinical studies evaluating PLX3397 reveal a metabolically stable drug that displays extensive protein binding. Clinically relevant drug-drug interactions are not anticipated based upon experimental evidence of negligible CYP inhibition or induction in vitro.

7.4 PLX3397 Nonclinical Toxicology, Genotoxicity and Safety Pharmacology

After establishing dose-response systemic exposure data with gavage formulations of PLX3397, the toxicology was evaluated in non-GLP repeat dose and GLP 28-day repeat-dose toxicity studies in Sprague-Dawley rats and Beagle dogs. Standard GLP batteries of genotoxicity and safety pharmacology studies were also performed.

Results of the studies are presented below. In summary, a NOAEL for either species was not determined, based on body weight losses and several histological and/or gross morphological effects. However, the significant test article-related adverse effects (testes, ovaries, bone and bone marrow, hematology and lymphoid changes) are consistent with the pharmacological mechanism of action of PLX3397. Importantly, all of these findings were partially or fully reversible. There were no safety findings in the genotoxicity and safety pharmacology studies.

Please refer to the Investigator's Brochure for a more detailed description of the non-clinical toxicology and safety pharmacology studies.

7.4.1 Repeat-dose Toxicity in Rats

In rats administered PLX3397 by oral gavage for 7 days at doses of 30, 100, and 300 mg/kg/day, there were modest potential test article-related effects as follows: decreased WBC and hemoglobin, increased AST, ALT, alkaline phosphatase, increased liver and decreased spleen weights, bone marrow hematopoietic atrophy, and cystic corpora lutea. Under the conditions of this study the NOAEL was 30 mg/kg/day for males and females.

In the subsequent GLP 28-day study with a 14-day recovery period, Sprague-Dawley rats were dosed at 20, 60, and 200 mg/kg/day. Exposure increased as dosage was increased over the 20 to 200 mg/kg/day range for both sexes, with exposure in females tending to be modestly higher (9–34%, depending on dose) compared to males.

Non-adverse lower body weights and food consumption were noted for the 200 mg/kg/day group females. Body and food consumption effects resolved during the recovery period.

Changes in hematology parameters consisted of dose-related lower WBC, RBC, PT, aPTT, and lower reticulocyte counts in all test article-treated groups. At study day 43 recovery evaluation, the WBC counts had rebounded, the RBC mass partially recovered, reticulocyte counts were higher than the control group, and fibrinogen, PT, and APTT had resolved in the 200 mg/kg/day groups. Alterations in hematology are likely related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase. No effects on clinical chemistry were considered adverse.

Microscopic findings in endocrine and reproductive tissues included dose-related higher incidence and severity of hemorrhagic corpora luteal cysts in the ovaries in the 60 and 200 mg/kg/day females, dose-related higher incidence and/or severity of thyroid follicular cell hypertrophy in the 200 mg/kg/day groups. Minimal to moderate depletion of spermatogenic epithelium at study Day 28/29 was noted in the 60 and 200 mg/kg/day group males, and the 200 mg/kg/day group males were often completely devoid of spermatogonia and pachytene spermatocytes. Tubules in stages of elongation were frequently characterized by complete absence of prepachytene and pachytene spermatocytes and sertoli cell vacuolization was occasionally observed. At study Day 43, the 200 mg/kg/day group males had depletion of spermatogonic epithelium and mild to severe atrophy characterized by a depletion of spermatids,

however there was an increase in the spermatogonial population, which is reflected by the presence of significant numbers of early prepachytene (leptotene and zygotene) spermatocytes. Alterations in testes and ovaries are likely related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase.

There were macroscopic findings of discoloration/red areas of the ovaries in the 60 and 200 mg/kg/day females at primary necropsy, and soft/small testes in the 200 mg/kg/day group males at the recovery necropsy. Microscopic alterations included dose-related minimal to moderate subphyseal hyperostosis in the femur for the 60 and 200 mg/kg/day groups, minimal to moderate physeal hypertrophy in the femur for the 60 and 200 mg/kg/day groups, and dose-related reduction in the density of hematopoietic cells of all lineages within the bone marrow (sternum and femur). Alterations in bone parameters are likely related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase. Dose-related hepatocellular centrilobular hypertrophy was noted for the 200 mg/kg/day groups, and correlated with higher liver enzyme levels and higher liver weights, and a higher incidence and/or severity of chronic progressive nephropathy was noted for the 200 mg/kg/day groups. This finding is a normal spontaneous change in Sprague-Dawley rats and was noted in the vehicle control groups. Microscopic findings in the skin and lymphoid tissues included a dose-related higher incidence of minimal to mild myxomatous change in the skin/subcutis of all test article-treated groups, and lymphoid depletion of the cortex in the thymus in the 60 and 200 mg/kg/day groups.

The majority of alterations in morphologic pathology parameters, except for luteal cysts and chronic progressive nephropathy, partially or completely resolved following the recovery period. Luteal cysts reduced in severity, but remained higher than the control group in the 200 mg/kg/day group females. On the basis of observations made in this GLP-compliant study, a no-observed adverse effect level (NOAEL) for oral (gavage) administration of PLX3397 was not determined. This study also did not establish a lethal dose in 50% of rats LD_{50} or severely toxic dose in 10% of rats (STD10). However for the purposes of calculating a clinical starting dose for oncology, Plexxikon has assumed the highest dose tested in this study (200 mg/kg) to be the STD10.

7.4.2 Repeat-dose Toxicity in Dogs

In two pairs of Beagle dogs administered PLX3397 at a dose of 600 mg/kg BID (1200 mg/kg/day) for 7 days, findings included emesis and mild to moderate reduction of erythropoiesis in bone marrow. Mild body weight loss was likely secondary to emesis.

In the subsequent GLP toxicity study, groups of Beagle dogs were administered PLX3397 for 28 days at doses of 100, 300, and 1000 mg/kg/day which was then reduced to 50, 100, and 300 mg/kg/day after the first week due to lethargy, weight loss, and lack of food consumption in several high dose animals.

Mean exposure generally increased as dosage increased over the 50 to 1000 mg/kg/day range, but the range of exposure observed for individual animals within a dose group frequently overlapped between the dosages of 50 and 100 mg/kg/day and 300 and 1000 mg/kg/day doses. Exposure tended to be similar in males compared to females.

There were no test-article-related ophthalmic or macroscopic findings or effects on urinalysis, ECG or organ weight parameters.

Three dogs in the 1000/300 mg/kg/day group were euthanized in extremis on study Days 8, 15, and 17 due to prostration, tremors, impaired coordination, and tachypnea. Emesis was noted in all groups with an increased incidence in the 300/100 and 1000/300 mg/kg/day groups.

Modest body weight declines were observed for the 300/100 and 1000/300 mg/kg/day group; primarily from study Week 0 to 1. These changes correlated with decreased food consumption and were reversible during the recovery period.

There were no adverse test article related serum chemistry effects. Hypophosphatemia was noted in males at dosage levels >300/100 mg/kg/day and in females at doses >100/50 mg/kg/day. Elevated levels of PTH in the 300/100 and 1000/300 mg/kg/day groups may have contributed to the hypophosphatemia, but was reversible and not severe enough to be considered adverse. Additionally, Fms inhibition can reduce osteoclast differentiation and function, resulting in decreased bone resorption and decreased serum phosphate.

PLX3397 caused significant, partially reversible testicular atrophy at all three doses. The earliest changes, noted in two 1000/300 mg/kg/day group males euthanized in extremis, were severe, with diffuse spermatocytes and spermatid degeneration. At study Week 4, the atrophic tubules contained small numbers of retained spermatids and degenerate/multinucleate intra-luminal spermatids.

PLX3397-related alterations were less prominent in the ovary, possibly because most ovaries were immature. Follicular degeneration, characterized by large, distorted, antral follicles with extensive apoptosis of granulose cells and a peripheral stromal cell proliferation, was noted in two of three females administered 1000/300 mg/kg/day. There appeared to be an increased number of atretic follicles in one of two affected dogs. Alterations in testes and ovaries are likely related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase.

Bone marrow exhibited a dose-related minimal to mild hypocellularity. Following a 14-day recovery, the bone marrow from the 1000/300 mg/kg/day group was minimally hypercellular, demonstrating recovery. In the spleens, minimal to mild increased extramedullary hematopoiesis was noted in all dose groups. The extramedullary hematopoiesis was an expected physiologic response to the decreased RBC mass and regenerative anemia.

In the femur, minimal to moderate subphyseal hyperostosis was evident in dogs that received 300/100 and 1000/300 mg/kg/day. Hyperostosis was not evident at study Week 6. This lesion was characterized by a retention and elongation of the primary spongiosa beneath the physis and was considered a reversible consequence of pharmacologic effect on osteoclasts.

Lymphoid depletion was evident in the thymus, lymph nodes, Peyer's patches, and spleen more frequently, compared to vehicle controls. These effects were considered to be secondary to PLX3397-related nonspecific stress factors; however, an organ-specific test article-related effect on the lymphoid system cannot be excluded.

Minimal to mild valvular endocardiosis was occasionally noted in placebo- and PLX3397-treated dogs at study Weeks 4 and 6. Because this finding can occur spontaneously and a clear dose-response was not observed, it was likely not a direct PLX3397-related effect. Additionally minimal subendothelial myxomatous change was noted in four dogs treated with PLX3397 at the primary necropsy. This alteration was characterized by focal increases in proteoglycans near the luminal surface of the aorta. While regional variation in proteoglycan content was considered within normal limits and the change could have been part of the normal spectrum, a PLX3397-related effect cannot be ruled out. Importantly, no evidence of myxomatous change in the aorta was noted in the 28-day rat GLP toxicology study where high-dose unbound PLX3397 exposure was 18-fold that seen at the high-dose in the dog study.

In the kidneys, basophilic tubules were noted in the 100/50 (females only) 300/100 and 1000/300 mg/kg/day groups with no clear relationship to the PLX3397 dose administered. Basophilic tubules are a common spontaneous finding in control group dogs. The incidence of findings was within the range of those noted in the database of historical control groups. Thus the kidney findings were considered of uncertain relationship to the test article.

Changes in hematology parameters consisted of time- and dose-related declines in RBC mass and reticulocyte counts at 1000/300 and 300/100 mg/kg/day, which correlated with bone marrow hypocellularity resulting in a non-regenerative anemia at study Week 2. The anemia increased in severity at study Week 4, despite a rebound in absolute numbers of reticulocytes. These effects were considered adverse though reversible, based on partial recovery noted at study Week 6. Higher fibrinogen levels were also noted in all dose groups. Alterations in hematology are likely related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase.

Based on the results of this study, systemic toxicity of PLX3397 administered orally by gavage twice daily for 28 consecutive days was observed at dosage levels of 300/100 and 1000/300 mg/kg/day, as evidenced by mortality (1000/300 mg/kg/day), adverse clinical observations of emesis, and emesis-related findings, body weight losses with associated low food consumption, and microscopic findings of the testes, bone marrow, kidneys, spleen, and lymphoid depletion in the thymus. Therefore, a NOAEL was not determined. This study also did not establish a lethal dose in 50% of dogs LD_{50}.For the purposes of calculating a clinical starting

dose for oncology Plexxikon has defined the 300 mg/kg dose to be the highest non-severely toxic dose (HNSTD) in dogs.

7.4.3 Genotoxicity

No signs of genotoxicity were identified in a standard battery of tests (in vitro AMES and chromosomal aberration and in vivo micronucleus assays) conducted with PLX3397.

7.4.4 Safety Pharmacology

In GLP-compliant respiratory and central nervous system safety studies, the NOEL for PLX3397 was 200 mg/kg in rats. Additionally, three GLP-compliant safety pharmacology studies addressed the potential adverse cardiovascular or cardiac electrophysiological effects of PLX3397. When evaluated in a serum free hERG study, PLX3397 was shown to bind to the channel (IC_{50} 0.7 μM). However, in a follow-up cardiac Purkinje fiber study, no test article-related effects on repolarization, AP amplitude or speed of cardiac depolarization were observed. Furthermore, in a dog in vivo GLP cardiovascular safety study, all electrocardiographic parameters were qualitatively and quantitatively within normal limits, demonstrating that PLX3397 does not prolong cardiac repolarization up to the highest dose tested (1000 mg/kg).

7.5 PLX3397 Nonclinical Reproductive Toxicology

Three GLP embryo-fetal development reproductive toxicology studies have been performed, including dose-ranging studies in rats and rabbits, and a definitive rat study. In rats, 10 mg/kg/day was the NOAEL for both maternal and fetal toxicity. In rabbits, both maternal and fetal toxicities were identified at doses ≥60 mg/kg/day.

7.6 PLX3397 Previous Human Experience

The ongoing Phase 1 dose escalation study PLX108-01 in patients with solid tumor was designed to evaluate the safety and PK of PLX3397 administered orally in order to establish a maximum tolerated dose (MTD). As of June 2012, a total of 62 patients have been treated with PLX3397 PO, including 41 patients in the dose escalation cohorts and 21 patients in the Extension cohorts. The dose levels have been 200 mg/day (n = 3), 300 mg/day (n = 6), 400 mg/day (n = 6), 600 mg/day (n = 6), 900 mg/day (n = 7), 1000 mg/day (n = 7) and 1200 mg/day (n = 6). In summary, the T_{max} is approximately 2 hours, the mean elimination half-life is approximately 20 hours, and the mean accumulation ratio compared to Day 1 values is approximately 2-fold. In general, there is good dose proportionality, with increasing exposure with increasing dose. On Day 15, the $AUC_{0\text{-}24hr}$ was 62 uM•hr for the 200 mg/day dose group, 122 uM•hr for the 300 mg/day dose group, 98 uM•hr for the 400 mg/day dose group, 258 uM•hr for the 600 mg/day dose group, 254 uM•hr for the 900 mg/day dose group and 329 uM•hr for the 1200 mg/day dose group (pharmacokinetic data for the 1000 mg/day cohort is not currently available). Dose-limiting toxicities (DLTs) of Grade 3 AST elevation and Grade 4 neutropenia

occurred at 1200 mg/day. A 1000 mg/day cohort was opened and 1 out of 7 patients experienced a DLT (Grade 3 AST), establishing 1000 mg/day as the MTD.

There have been no safety signals in vital signs, physical examinations, or ECGs (including careful evaluation of potential QT prolongation). A reduction in hemoglobin (usually G1) has been observed in several patients, but this has not resulted in treatment discontinuation in any patients. There have been a total of 6 patients with DLTs, as follows: G3 increased INR (300 mg/day) in a patient on warfarin; G3 lymphopenia (600 mg/day), subsequently exempted as a DLT; G3 lymphopenia and G4 hyponatremia (600 mg/day); G3 AST (1000 mg/day); G3 AST (1200 mg/day) which recovered after study drug discontinuation; and G4 neutropenia (1200 mg/day) which recovered after holding study drug and management with G-CSF. As this is a population of patients with metastatic solid tumors that have been heavily pretreated with cytotoxic therapies, adverse events are anticipated due to either the disease or previous treatments. The most common adverse events (AEs) have been fatigue, decreased appetite and nausea. Please see the Investigator's Brochure for more details on adverse events and tolerability.

Response biomarkers are being assayed in order to profile the inhibitory activity of PLX3397 on Fms and Kit activity as a function of dose and exposure. These biomarkers include circulating tumor cells (CTCs) and CD14+/CD16+ pro-inflammatory monocyte cell numbers; IL-6, IL-1β, MMP3 concentrations; and markers of osteoclast activity. Most of the soluble markers are not elevated at baseline in the patients treated to date, so no decrease with treatment can be anticipated. However, in 5 patients with elevated CTC counts at baseline, 3 patients have shown a clinically relevant reduction during treatment with PLX3397. Marked reductions in the CD14+/CD16+ cell populations have also been observed in the majority of patients, with no change in the remainder.

8.0 STUDY OBJECTIVES

As described in Section 7.1, there is a strong rationale for combining PLX3397 and paclitaxel for the treatment of advanced solid tumors, particularly breast cancer.

This trial is designed as a 3-part study: **Part 1** (Phase 1b), to explore the safety of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D; **Part 2**, to determine the efficacy and safety of the PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, non-resectable solid tumors; and **Part 3**, to determine the efficacy and safety of PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.

Part 1 (Phase 1b)

Primary Objective:

- To explore the safety and tolerability of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D

Secondary Objectives:

- To explore the efficacy and pharmacokinetics (PK) of PLX3397 in combination with paclitaxel in patients with advanced solid tumors.

Part 2

Primary Objective:

- To confirm the safety and tolerability of PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors

Secondary Objective:

- To explore the efficacy of PLX3397 in combination with paclitaxel in patients with advanced solid tumors

Parts 1 and 2

Exploratory Objectives:

- To correlate the change in CSF-1 levels during treatment with specific dose levels of PLX3397
- To identify new biomarkers of clinical activity

Part 3

Primary Objective:

- To determine the efficacy of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

Secondary Objectives:

- To evaluate the safety and tolerability of PLX3397 in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
- To explore the effect of PLX3397 on cancer tissue and blood biomarkers

9.0 DESIGN

9.1 Description

Part 1:

This is a nonrandomized, Phase 1b open-label, sequential dose escalation trial of PLX3397 plus paclitaxel. The study employs a traditional 3+3 design. Treatment with PLX3397 will consist of continuous oral administration and enrollment will begin at the 600 mg/day dose level for 28 days. Paclitaxel will be administered once weekly (±48 hours). The planned schedule for PLX3397 dose escalations is shown in Table 2. For doses higher than 1000 mg/day, the dose escalation increment may be adjusted based on the observed toxicity and systemic exposure at the previous dose level. However, the maximum dosing increment will be 50%.

Table 2: Planned Dose Escalation Schedule

Dose Level	Treatment	
	PLX3397 BID	**Paclitaxel**
Level -1	400 mg/day (200 mg PO BID) Days 1–28	80 mg/m2, ~ -60 min IV Days 1, 8, 15 and 22
Level 0 **(Starting Level)**	600 mg/day (300 mg PO BID for 100 mg capsules) (400 mg PO a.m.; 200 mg PO p.m. for 200 mg capsules) Days 1–28	80 mg/m2, ~60 min IV Days 1, 8, 15 and 22
Level 1	800 mg/day PO (400 mg PO BID) Days 1–28	80 mg/m2, ~60 min IV Days 1, 8, 15 and 22
Level 2	1000 mg/day PO (500 mg PO BID for 100 mg capsules) (600 mg PO a.m.; 400 mg PO p.m. for 200 mg capsules) Days 1–28	80 mg/m2, ~60 min IV Days 1, 8, 15 and 22
Level 3	1200 mg/day PO (600 mg PO BID)	80 mg/m2, ~60 min IV Days 1, 8, 15 and 22
Level 4	1600 mg/day PO (800 mg PO BID)	80 mg/m2, ~60 min IV Days 1, 8, 15 and 22
Level 5	2000 mg/day PO (1000 mg PO BID)	80 mg/m2, ~60 min IV Days 1, 8, 15 and 22

Each dose level cohort will enroll 3–6 patients per dose level. Enrollment into the next higher dose level will begin only if the first three patients enrolled into the cohort complete the 28-day observation period without the occurrence of a Dose-Limiting Toxicity (DLT) (Section 13.12). If one of the three initial patients at a given dose level experiences a DLT, the cohort at this dose level will be expanded to include an additional 3 patients (6 patients total).

Patients who discontinue treatment in Cycle 1 for any reason other than treatment-related or dose-limiting toxicity may be replaced. Patients who experience an allergic reaction to paclitaxel that precludes further dosing (i.e., ≥Grade 3) will be removed from the study and may also be replaced.

Intrapatient dose escalations will not be permitted. If ≥2/6 patients experience a DLT, then dose escalation will be stopped. The preceding dose level will be considered the MTD and, therefore, the RP2D.

Part 2:

This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (including all RP2D-treated patients

from **Part 1** and **Part 2**). The candidate population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.

Part 3:

This is a nonrandomized, open-label study of PLX3397 administered at the RP2D (600 mg BID) in combination with paclitaxel in approximately 30 patients. The candidate population will be patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Patients must be resistant or refractory to prior platinum-based standard care systemic regimens or refractory to primary treatment with a platinum-containing regimen. Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms: 1) daily PLX3397 600 mg BID; 2) weekly paclitaxel; and 3) daily PLX3397 600 mg BID and weekly paclitaxel. Cancer tissue for biomarkers will be obtained during Screening and during the period from Cycle 1 Day 21 to Cycle 1 Day 35. If the second biopsy in Cycle 1 is delayed beyond Day 28, patients will have a Cycle 1 Day 28 visit for paclitaxel administration (performed weekly), during which procedures will be the same as the Cycle 1 Day 22 visit. Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with daily PLX3397 600 mg BID and weekly paclitaxel. Cycle 2 and all subsequent cycles will be 28-day cycles. A blood sample for plasma PD and biomarkers will be obtained pre-PLX3397 and paclitaxel dosing on Cycle 1 Day 1, Cycle 1 Day 15, Day 1 of all subsequent cycles, and the End-of-Study Visit. CA-125 sampling requirements include 2 pre-treatment samples: the first sample within 3 months of starting therapy and a second sample within 1 week of Cycle 1 Day 1. Subsequent samples are collected on the first day of each cycle starting with Cycle 2 Day 1 and at the End-of-Study Visit.

9.2 Route and Regimen

Part 1:

PLX3397 will be administered orally, twice daily (BID) in capsule form using a continuous dosing regimen. The BID regimen is recommended at higher dose levels (e.g., ≥600 mg/day) to reduce the capsule load and minimize intra-day drug level fluctuations. The starting dose of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%.

A fixed dose level of paclitaxel 80 mg/m^2 will be administered intravenously, once weekly (±48 hours). Patients must receive at least 3 of 4 paclitaxel doses during the DLT period (i.e., Cycle 1) in order to be considered evaluable for DLT, unless doses are missed due to a DLT. One dose of paclitaxel may be skipped per Cycle for subsequent cycles (i.e., Cycle 2+) per Investigator discretion and/or patient preference. In general, two consecutive doses of paclitaxel should not be skipped.

Part 2:

PLX3397 will be administered orally, BID using a continuous dosing regimen. The dose of PLX3397 will be the RP2D. There will be no dose escalation. Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. One paclitaxel dose may be omitted per cycle by physician discretion after Cycle 1.

Part 3:

Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms:

1) PLX3397 600 mg BID using a continuous dosing regimen
2) Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes
3) PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes

Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with PLX3397.

Part 1, Part 2, and Part 3:

Study treatment will be provided until disease progression, unacceptable or dose-limiting toxicity, death, withdrawal of consent, study termination by Sponsor, or if the Investigator and patient agree that it is in the patient's best interests to discontinue.

9.3 Paclitaxel Premedications

A paclitaxel premedication regimen is recommended, but not required and should be provided per institutional guidelines. The premedication regimen may consist of the following agents:

- Intravenous dexamethasone (10 mg, or physician-selected dose), or other equivalent steroid, <60 minutes prior to paclitaxel. This may be tapered with subsequent doses per investigator discretion.

- Intravenous famotidine, 20 mg; or other equivalent H_2-antagonist (e.g., ranitidine 50 mg IV or cimetidine 300 mg IV), 30–60 minutes prior to paclitaxel.

- Intravenous diphenhydramine, 12.5–50 mg IV, 30–60 minutes prior to paclitaxel. Diphenhydramine can be excluded with subsequent doses per investigator discretion.

9.4 Number of Patients

Part 1:

Enrollment is planned to include approximately 30 patients from 3–4 sites. The total number of patients to be enrolled will depend on the number of cohorts and whether a cohort requires 3 or 6 patients. If a patient does not receive at least 21 days of PLX3397 during the first cycle or does not receive at least 3 of 4 doses of paclitaxel in the first cycle **for reasons other than a DLT**, the patient may be replaced.

Part 2:

Enrollment is planned to include approximately 30 patients (including all RP2D-treated patients from **Part 1** and **Part 2**) recruited from 3 sites.

Part 1 and Part 2:

Patients who do not receive the requisite PLX3397 and/or paclitaxel doses in Cycle 1 due to anything other than treatment-related and/or dose-limiting toxicity may be replaced. Patients who experience an allergic reaction to paclitaxel that precludes further dosing (i.e., ≥Grade 3) will be removed from the study and may also be replaced.

Part 3:

Enrollment is planned to include up to approximately 30 patients to accrue 18 patients who can provide pretreatment and end-of-Cycle 1 cancer tissue and are evaluable for determining response using RECIST 1.1 criteria. Patients unable to provide the sequential cancer tissue samples or non-evaluable for response using RECIST criteria will be replaced.

9.5 Number of Study Centers

The study will be performed at 3–4 investigational sites for Parts 1 and 2 and at approximately 9 investigational sites for Part 3.

9.6 Duration of Patient Participation

Each patient will be offered continued dosing with the PLX3397 + paclitaxel combination as long as it is well tolerated and both the Investigator and Sponsor agree that the patient is clinically benefitting from treatment. Reasons for study discontinuation include, but are not limited to, the following:

- Unacceptable or Dose-Limiting Toxicity
- Disease Progression

- Death
- Voluntary withdrawal of consent
- Non-compliance to study procedures and requirements
- Investigator decision
- Sponsor decision to terminate the study

9.7 Duration of Study

The duration of the study will depend on the recruitment rate and the duration of treatment for those patients enrolled.

10.0 SELECTION OF STUDY POPULATION

All patients must participate in the consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. No protocol-specific procedures, including screening procedures that are not part of standard-of-care, are to be performed until the patient has signed and dated an institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form. Standard-of-care procedures performed prior to informed consent may be collected as part of screening data if the procedures occurred within the protocol-specified timeframe. The study begins with the signing and dating of the informed consent form. Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

10.1 Inclusion Criteria

1. Patients with:

    a. **Part 1:** an advanced, incurable solid tumor

    b. **Part 2:** an advanced, incurable solid tumor for whom a taxane would be considered a reasonable chemotherapy option

    c. **Part 3:** advanced, metastatic or non-resectable epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer with:

        i. platinum-resistant cancer, defined as disease that responded to a platinum-containing chemotherapy regimen, but demonstrated recurrence within six months following the completion of that platinum-containing regimen,

    OR

ii. platinum-refractory cancer, defined as disease failed to achieve at least a partial response to a platinum-containing regimen (i.e., stable disease or actual disease progression),

AND

iii. have not been treated with a taxane within 6 months of C1D1,

AND

iv. have not been treated with weekly paclitaxel after first-line treatment in which weekly paclitaxel plus a platinum is permitted

2. **Part 3:** Patients must have target (≥2 cm diameter) or non-target lesion cancer that is accessible for 2-3 core biopsies during Screening after CT imaging and all other screening tests and procedures have been completed and during the period from Cycle 1 Day 21 to Cycle 1 Day 35

3. Patients with stable brain metastases are eligible for this trial. However, patients must not have required steroid treatment for their brain metastases within 30 days of Screening.

4. Bone-directed therapy (e.g., bisphosphonates or denosumab) is permitted. However, patients should not have started bone-directed therapy within 2 weeks of C1D1, and new bone-directed therapy should not be initiated during the first 4 weeks of study (i.e., Cycle 1)

5. Washout from any prior investigational therapy of at least five times the $T_{1/2}$ prior to C1D1

6. Washout from any prior biologic or targeted therapy at least 4 weeks or five times the $T_{1/2}$ (whichever is shorter) prior to C1D1

7. Washout from prior chemotherapy of at least 2 weeks or 1 elimination half-life, whichever is longer, prior to C1D1

8. Washout from prior hormonal therapy of at least 2 weeks prior to C1D1

9. Washout of at least 2 weeks from the most recent radiation treatment prior to C1D1

10. Resolution of all prior treatment-related toxicities to Grade 1 or less, except for Grade 2 fatigue or alopecia prior to C1D1

11. Age eighteen years or older

12. ECOG performance status 0–2, inclusive

13. Anticipated life expectancy of at least 12 weeks

14. Adequate bone marrow reserve: ANC ≥1500/mm^3, platelets ≥100,000/mm^3

15. Adequate renal function: serum creatinine <1.5 x ULN or calculated CrCl >60 mL/min using Cockcroft-Gault formula

    GFR = [(140-age)•(weight in kg)•(0.85 if female)]/(72•Cr)

16. Adequate hepatic function: AST and ALT <2.5 x ULN, Total and Direct Bilirubin <1.5 x ULN. However, in the presence of liver metastases, AST and ALT must be <5 x ULN

17. Cardiac ejection fraction ≥50%, and QTcF<450 ms (males) or <470 ms (females) on ECG at Baseline

    Fridericia's Formula: $QTcF = (QT)/RR^{0.33}$

18. Able to swallow capsules and maintain adequate hydration

19. Ability to give written informed consent and willing to comply with the requirements of the protocol; and for **Part 3**, to give written informed consent for 2 cancer biopsy procedures

20. Women of child-bearing potential must agree to use an effective method of birth control during treatment and for three months after receiving their last dose of study drug. Fertile men must also agree to use an acceptable method of birth control while on study drug and for at least 3 months after last dose (see Attachment 4).

10.2 Exclusion Criteria

1. Presence of an active secondary malignancy

   - Patients with a non-melanomatous, in situ malignancy or disease that is completely resectable with surgery may be considered after discussion with the Medical Monitor

   - Patients with a completely treated prior malignancy with no evidence of disease for ≥3 years are eligible

2. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant small bowel resection that would preclude adequate absorption of PLX3397

3. Ongoing treatment with any other investigational therapy

4. Prior anaphylactic or severe hypersensitivity reaction to paclitaxel or Cremophor-containing agent

5. Persistent grade 2 fatigue at Baseline

6. Severe, concurrent illness including congestive heart failure, significant cardiac disease and uncontrolled hypertension, that would likely prevent the patient from being able to comply with the study protocol

7. Active untreated infection

8. Known chronic active Hepatitis B or C, or HIV infection

9. The presence of a medical or psychiatric condition that, in the opinion of the Principal Investigator, makes the patient inappropriate for inclusion in this study

10.3 Screen Failures

Patients who sign an informed consent form, are not assigned to a treatment, and do not receive test article are defined as screen failures. For all screen failures, the investigator will enter the screening number, patient initials and reason(s) for screen failure into a screen failure log. This data will also be retained in the investigator's study files and can be printed by the site in log format at the end of the study.

In Part 3, patient data will be collected in the electronic data capture (EDC) system from the date the biopsy is performed during screening. Data will not be collected in the EDC for patients who are screen failures and have not had a biopsy assessment.

11.0 PRIOR TREATMENT

Reasonable efforts will be made to determine all relevant treatment received by the patient within 28 days before administration of the test article. All previous cancer treatments should be recorded. Relevant information must be recorded on the patient's electronic case report form (eCRF).This should include the name of the procedure or drug and other information required on the eCRF.

12.0 CONCOMITANT TREATMENT

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 adverse event), 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.

Prophylaxis or medical management for nausea and vomiting with antiemetics is encouraged, particularly in patients with a history of nausea or vomiting with prior taxane therapy.

Although PLX3397 does not appear to inhibit CYP drug-metabolizing enzymes to an important extent, caution is warranted when administering PLX3397 to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. Notably, two minor metabolites of paclitaxel, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*dihydroxypaclitaxel, are metabolized by CYP3A4. It is not known whether systemic exposure to these medications will demonstrate an increase while patients are receiving PLX3397.

Of the five major CYP isoforms, 3A4 (BFC) may be involved in phase I (i.e., first pass) metabolism of PLX3397, with possibly CYP1A2 playing a minor role. Until information regarding exposure-toxicity and exposure-response relationships are available with PLX3397, concomitant CYP3A4 inhibitors and inducers should be administered with caution, in the event they alter the systemic exposure to PLX3397 (see Attachment 3 for a list of common CYP3A4 inhibitors and inducers).In general, strong inhibitors or inducers of CYP3A4 should be avoided unless absolutely clinically necessary and without effective alternatives. These include anticonvulsants, mycin antimicrobials, and antiretrovirals. Some common examples include inhibitors such as erythromycin, fluoxetine, gemfibrozil, and inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.

Filgrastim growth factor support is encouraged for ANC <1500/mm^3 and may be used at the discretion of the Principal Investigator in consultation with the Medical Monitor. Growth factors may be administered throughout the study, including during Cycle 1, in order to maintain adequate blood counts. For patients whose ANC is between 1500–2000 cells/mm^3, Filgrastim may be administered from days 2–5 (total of 4 days) after the most recent paclitaxel infusion. Filgrastim is not permitted within 24 hours prior to or following any paclitaxel infusion. Pegfilgrastim (Neulasta) is not permitted in this study.

13.0 PROCEDURES

13.1 Screening Evaluation

The following Screening assessments must be performed **within 28 days** before study drug administration on C1D1:

1. Sign and date an IRB/IEC-approved informed consent form before any study-specific screening procedures are performed

2. Demographic information including date of birth, sex and ethnic origin

3. Medical history including significant medical procedures
4. Prior treatment for cancer
5. Height (cm) and weight (kg)
6. Vital signs (sitting blood pressure, pulse rate, respiratory rate, and temperature [°F])
7. Standard 12-lead ECG, including QTcF
8. Trans-thoracic echocardiogram or MUGA
9. Imaging for baseline tumor status
10. **Part 3 only:** Cancer tissue [2-3 core biopsies of target (≥2 cm diameter] or non-target lesions) for biomarkers after CT imaging and all other screening tests and procedures have been completed
11. **Part 3 only:** CA-125 sampling within 3 months of starting therapy
12. Recording of concomitant medications
13. ECOG Performance status assessment
14. **Part 3 only:** AE and serious adverse event (SAE) reporting will commence when the 2-3 core biopsies are obtained during Screening**.**

The following Screening assessments must be performed **within 14 days** before study drug administration on C1D1:

- Full physical examination
- Clinical laboratory evaluation (hematology and chemistry)
- For women of child-bearing potential, urine pregnancy test

The following Screening assessments must be performed **within 7 days** before study drug administration on Cycle 1Day 1:

- **Part 3 only:** CA-125 sampling

A patient who meets all of the inclusion criteria will continue on in the study. Screen failures will be marked in the EDC system.

13.2 Pre-Treatment (Baseline): Cycle 1 Day 1

Patients will return to the clinic on C1D1 and will undergo the following procedures prior to dosing:

1. Recording of concomitant medications
2. Vital signs and weight
3. Symptom-directed physical exam
4. ECOG Performance status
5. Clinical laboratory evaluation (hematology and chemistry)
6. Pre-PLX3397 dose blood sample collection for plasma PK **(Part 1 and Part 3 only)** and PD biomarker analyses
7. Pre-PLX3397 dose whole blood sample collection for CD14/CD16 monocyte analysis. Per instructions in the Laboratory Manual, this sample is time sensitive and must be shipped out the same day as the collection, refrigerated but not frozen.
8. **Part 3 only:** Pre-PLX3397 dose whole blood sample collection for myeloid-derived suppressor cell (MDSC)
9. **Part 1, Part 2, and Part 3 (PLX3397 only and PLX3397 + paclitaxel arms):** PLX3397 administration. Patients should fast for at least 1 hour prior to and after PLX3397 administration (see Section 14.1.1).
10. **Part 1, Part 2, and Part 3 (paclitaxel only and PLX3397 + paclitaxel arms):** Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies)
11. **Part 1, Part 2,and Part 3 (paclitaxel only and PLX3397 + paclitaxel arms):** Paclitaxel administration

13.3 Post-Treatment: Cycle 1 Day 1

Following receipt of all study drugs, patients will be evaluated for adverse events and PLX3397 compliance.

13.4 Cycle 1 Day 8 (±48 hours)

At the C1D8 visit, patients will return to the clinic and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. PLX3397 compliance evaluation
4. Clinical laboratory values (hematology and chemistry)
5. PLX3397 administration (may be taken prior to the clinic visit; patients must fast for at least 1 hour prior to and after administration per instructions in Section 14.1.1)
6. Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies)
7. Paclitaxel administration

13.5 Pre-treatment Cycle 1 Day 15 (±48 hours)

At the C1D15 visit, patients will return to the clinic and undergo the following procedures:

1. Pre-PLX3397 dose blood sample for PK **(Part 1 and Part 3 only)**
2. AE monitoring
3. Recording of concomitant medications
4. PLX3397 compliance evaluation
5. Clinical laboratory values (hematology and chemistry)
6. 12-lead standard ECG, including QTcF
7. Pre-PLX3397 dose whole blood sample collection for CD14/CD16 monocyte analysis. Per instructions in the Laboratory Manual, this sample is time sensitive and must be shipped out the same day as the collection, refrigerated but not frozen.
8. **Part 3 only:** Pre-PLX3397 dose whole blood sample collection for MDSC
9. **Part 3 only:** Pre-PLX3397 dose blood for plasma PK and biomarkers
10. PLX3397 administration (must be administered in the clinic; patients must fast for at least 1 hour prior to and after administration per instructions in Section 14.1.1).
11. Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies).

12. Paclitaxel administration.

13.6 Post-treatment Cycle 1 Day 15 (±48 hours)

Following receipt of all study drugs, patients will undergo the following:

1. Post-dose blood sample for PK **(Part 1 only)** at 2 and 4 hours following PLX3397 administration
2. Post-dose blood sample for PK (**Part 3 only**) at 2, 4, and 6 hours following PLX3397 administration
3. AE monitoring

13.7 Cycle 1 Day 22 (±48 hours)

At the C1D22 visit, patients will return to the clinic and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. PLX3397 compliance evaluation
4. Clinical laboratory values (hematology and chemistry)
5. PLX3397 administration (may be taken prior to the clinic visit; patients must fast for at least 1 hour prior to and after administration per instructions in Section 14.1.1)
6. Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies)
7. Paclitaxel administration.

13.8 Part 3 Only: Cycle 1 Day 28 ± 7 days (Cycle 1 Day 21 to Cycle 1 Day 35)

- Cancer tissue [2-3 core biopsies of target (≥2 cm diameter) or non-target lesions] for biomarkers

13.9 All Subsequent Cycles, Day 1 (±48 hours)

At all subsequent D1 visits, patients will return to the clinic and undergo the following procedures:

1. AE monitoring

2. Recording of concomitant medications
3. PLX3397 compliance
4. Vital signs and weight
5. Symptom-directed physical exam
6. Clinical laboratory values (hematology and chemistry)
7. Blood sample for plasma PK **(Part 1 and Part 3 only)** and PD biomarker analyses taken prior to PLX3397 dose
8. **Part 3 only:** CA-125 sampling
9. ECOG performance status
10. PLX3397 administration(may be taken prior to the clinic visit; patients must fast for at least 1 hour prior to and after administration per instructions in Section 14.1.1)
11. Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies)
12. Paclitaxel administration (may be skipped based on 3-week administration schedule)

13.10 All Subsequent Cycles, Days 8, 15 and 22 (±48 hours)

At all subsequent Day 8, 15and 22 visits, patients will return to the clinic and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. PLX3397 compliance
4. Clinical laboratory values (hematology only required prior to paclitaxel administration)
5. **Cycle 2 only:** serum chemistry only required prior to paclitaxel administration for **Part 3 – all arms**
6. **Cycle 3 only:** serum chemistry only required for Part 3 **Lead-in Paclitaxel Alone Arm**
7. PLX3397 administration (may be taken prior to the clinic visit; patients must fast for at least 1 hour prior to and after administration per instructions in Section 14.1.1)

8. Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies)

9. Paclitaxel administration (may be skipped based on 3-week administration schedule)

13.11 Other Schedules

PLX3397 will be administered twice daily (BID) in each 28-day cycle. Imaging for tumor assessments will be performed either every 8 weeks or as clinically indicated.

13.12 End of Study

All patients discontinuing study treatment for any reason should return to the clinic within 28 days following their last dose of the study drug combination and prior to receiving new antitumor therapy for the following procedures:

1. AE monitoring

2. Recording of concomitant medications

3. PLX3397 compliance

4. Vital signs and weight

5. Symptom-directed physical examination

6. ECOG performance status

7. Clinical laboratory values (hematology, chemistry, and urine pregnancy test for women of child-bearing potential)

8. **Part 3 only:** Blood for plasma PK and biomarkers

9. **Part 3 only:** CA-125 sampling

10. 12-lead ECG, including QTcF

11. End of Study imaging for tumor assessments should be obtained for patients who go off study for reasons other than radiographic disease progression

13.13 Dose-Limiting Toxicities (Part 1 only)

A Dose Limiting Toxicity (DLT) is any treatment-related adverse event that meets the criteria below that occurs **within the first 28 days of combination therapy**. Patients must receive at

least 21 days of PLX3397 and at least 3 of 4 doses of paclitaxel during the first cycle in order to be considered evaluable for DLT (unless the missed doses are due to a DLT).

Hematologic DLTs

- Grade 4 neutropenia lasting for ≥7 days in duration
- Grade 4 thrombocytopenia (platelets ≤25.0/μL)
- Grade 3 thrombocytopenia with bleeding

Other DLTs

Any CTCAEv4 Grade ≥3 other toxicity, **unless the event is clearly unrelated** to treatment with PLX3397 in combination with weekly standard fixed dosing of paclitaxel EXCEPT the following:

- Allergic reaction to paclitaxel
- Grade ≥3 nausea, vomiting, or diarrhea that resolves to Grade ≤2 within 48 hours, with or without medical intervention or prophylaxis
- Grade 3 fatigue that resolves to Grade ≤2 within 14 days
- Grade ≥3 hyperglycemia
- Transient (<14 days) increase in LFTs (of ≤one Grade in severity) compared to baseline levels in patients with baseline liver metastases.
- Grade 3 peripheral neuropathy in patients with baseline ≥Grade 1 peripheral neuropathy or a history of chemotherapy-associated peripheral neuropathy
- Grade 3 myalgia or arthralgia in patients with baseline ≥Grade 1 myalgia or arthralgia
- Grade 3 rash for which symptoms are easily managed with supportive care and no evidence of superinfection or limitation of self-care ADLs.

13.14 Dose Modifications

13.14.1 PLX3397 Dose Modifications

During **Part 1** PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 **only if a patient experiences a DLT.** PLX3397 interruptions during Cycle 1 are also permitted for Grade 3 vomiting that persists despite optimal supportive care. If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be

permitted at the discretion of the Investigator and in consultation with the Medical Monitor. After C1D28, dose reductions or interruptions for adverse events may take place at any time.

During **Part 2 and Part 3**: PLX3397 dose reductions or interruptions for adverse events may take place at any time.

For **Part 1, Part 2, and Part 3,** guidelines for dosage modification for PLX3397–related toxicities as well as guidelines for their management are noted in Table 3. Please contact the Medical Monitor prior to making any dose modifications. Dose reductions should occur in increments of 200 mg. These parameters are only suggestions and are not intended to supersede the clinical judgment of the treating physician. All adjustments should be made in consultation with the Medical Monitor.

Table 3: Dose Modifications Guidelines for PLX3397

Toxicity Grade (CTCAE v4)	PLX3397 Dose Changes During Current Treatment Period	Dose Adjustments for Resumption of Treatment[a]
Hematologic Toxicity		
Grade 3 or 4 neutropenia		
1st Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; provide growth factor support	If recovered to ANC ≥1 × 10^9/L in ≤7 days, resume at same dose.
		If ANC does not recover to ≥1 × 10^9/L after 7 days, reduce dose by 200 mg per day.
2nd Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; provide growth factor support	If recovered to ANC ≥1 × 10^9/L in ≤7 days, reduce dose by 200 mg.
		If ANC does not recover to ≥1 × 10^9/L after 7 days, reduce dose by an additional 200 mg per day.
3rd Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; provide growth factor support	If recovered to ANC ≥1 × 10^9/L in ≤7 days, reduce dose by 200 mg.
		If ANC does not recover to ≥1 × 10^9/L after 7 days, discontinue permanently.
4th Appearance	Discontinue permanently	N/A
Grade 3 or Grade 4 febrile neutropenia		
1st Appearance	Interrupt until ANC and fever recovery; provide growth factor support	Once resolved to ANC ≥1000 × 10^6/L and T ≤38°C, reduce dose by 200 mg per day.
2nd Appearance	Interrupt until ANC and fever recover; provide growth factor support	Once resolved to ANC ≥1000 × 10^6/L and T ≤38°C, reduce dose by an additional 200 mg per day.
3rd Appearance	Discontinue permanently	N/A

Toxicity Grade (CTCAE v4)	PLX3397 Dose Changes During Current Treatment Period	Dose Adjustments for Resumption of Treatment[a]
Grade 4 thrombocytopenia		
1st Appearance	Interrupt until PLT ≥75x10^9/L	Reintroduce at same dose
2nd Appearance	Interrupt until PLT ≥75x10^9/L	If PLT does not recover to ≥75 × 10^9/L after 7 days, reduce dose by 200 mg.
3rd Appearance	Interrupt until PLT ≥75x10^9/L	Reduce dose by an additional 200 mg per day
4th Appearance	Discontinue permanently	N/A
Other Related Toxicities (≥Grade 3), with the exception of liver-enzyme abnormalities (for which, see Transaminase increases box below)		
Other Related Grade 3 (start symptomatic treatment when possible)		
1st Appearance [b]	Interrupt until resolved (grade 0-1)	If recover <5 days, resume at same dose. Reduce by 200 mg if symptoms persist for ≥5 days despite supportive management [c]
2nd Appearance	Interrupt until resolved (grade 0-1)	Reduce by an additional 200 mg.
3rd Appearance	Discontinue permanently	N/A
Other Related Grade 4 (start symptomatic treatment when possible)		
1st Appearance	Interrupt until resolved (grade 0-1)	Reduce by 200 mg
2nd Appearance	Discontinue permanently	N/A
Transaminase increases and enzyme abnormalities		
• 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 • ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).	Dose hold and immediately discuss with Medical Monitor.	N/A

Toxicity Grade (CTCAE v4)	PLX3397 Dose Changes During Current Treatment Period	Dose Adjustments for Resumption of Treatment[a]
Prolonged QTcF		
QTcF >500 msec on at least 2 separate ECGs (i.e., Grade 3).	Hold PLX3397 until recovery to QTcF ≤500 msec.	Upon recovery to QTcF ≤500 msec (Grade ≤2), restart at a reduced dose (minimum reduction decrement of 200 mg). Monitor ECG and electrolytes, including potassium, magnesium, and calcium, after dose modification of PLX3397 for QTcF prolongation
QTcF interval remains >500 msec and increased >60 msec from pretreatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias).	Permanently discontinue PLX3397.	N/A.

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

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

[b] Except for cases of Grade 3 emesis.

[c] Except in cases of Grade 3 symptomatic rash.

Dose interruptions for Grade 2 non-hematologic 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.

For Grade 3 emesis that persists despite optimal supportive care, PLX3397 doses should be held until resolution to Grade 2 or less.

For cases of Grade 3 symptomatic rash that persists despite medical intervention, PLX3397 doses should be held until resolution to Grade 2 or less. Upon reintroduction of PLX3397, the dose level should be reduced by 200 mg/day.

13.14.2 Paclitaxel Dose Modifications

Dose modifications or interruptions of paclitaxel are not permitted in **Part 1**, Cycle 1 unless the patient experiences a DLT. Patients must receive the first 4 scheduled Paclitaxel doses, but may skip 1 dose per Cycle beginning at Cycle 2 per Investigator discretion and/or patient preference.

In order to receive weekly paclitaxel treatment, the following criteria must be met:

- ANC $\geq 1000/mm^3$

- Platelets ≥75,000/mm^3

If these criteria are not met, treatment must be delayed until counts recover to this level. Paclitaxel should be held for all instances of febrile neutropenia (ANC <1000/mm^3). Filgrastim growth factor support is encouraged for ANC <1500/mm^3 and may be used at the discretion of the treating physician in order to maintain adequate blood counts EXCEPT during the first cycle. Filgrastim is not permitted within 24 hours prior to or following any paclitaxel infusion. Pegfilgrastim (Neulasta) is not permitted in this study.

If paclitaxel is held due to neutropenia, PLX3397 should still be administered. At least 21 days of PLX3397 and 3 of the 4 doses of paclitaxel must be administered in the first cycle unless the patient experiences a DLT.

For **Part 1, Cycle 2 and subsequent cycles** and for **Part 2** and **Part 3**, other dose modifications for paclitaxel will be in accordance with the product label.

13.15 Discontinuation of Treatment and Withdrawal of Patients

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse event, disease progression, patient request, investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor. When a patient discontinues or is withdrawn, the investigator will notify the Sponsor (or designee) and should perform the procedures indicated in the End of Study column in the study flow chart within 28 days after discontinuation of study drug and prior to initiation of any new anti-tumor therapy. If a patient is withdrawn on a non-PK day, a PK sample should be obtained. All efforts should be made to obtain follow-up information for patients who discontinue their participation in or are withdrawn from the study.

Patients withdrawn from the study may be replaced at the discretion of the medical monitor and the investigator. PLX3397 and/or Paclitaxel administration may be discontinued for an adverse event or at the discretion of the investigator. Patients who discontinue treatment for reasons other than treatment-related and/or dose-limiting toxicity or with a clinically significant allergic reaction to paclitaxel that precludes further treatment (i.e., ≥Grade 3) may be replaced.

14.0 TEST ARTICLES

14.1 PLX3397

14.1.1 PLX3397 Administration

PLX3397 will be administered orally using a capsule formulation (either 100 mg or 200 mg per capsule). PLX3397 will be administered only to patients who have signed and dated an informed consent form. PLX3397 will be administered on Days 1 through 28 of each 28-day cycle, beginning on C1D1 (baseline). PLX3397 should be taken orally with 240 mL (8 oz.) of water in the fasting state. **The patient should fast at least 1 hour before administration and 1 hour**

after administration of PLX3397. Patients will be permitted to eat a low-fat, bland snack (e.g., crackers, toast, tea) during the fasting period if needed. Questions related to permitted pre- or post-dose snacks should be directed to the Medical Monitor.

PLX3397 should be taken by the patient at approximately the same time of day. The time between BID doses should be approximately 12 hours. Dosing may occur once daily (QD) under certain circumstances (e.g., dose reductions) and at the discretion of the Investigator in consultation with the Medical Monitor. QD dosing should be approximately 24 hours apart.

For **Part 1** only on C1D1, C1D15, and the first day of all subsequent cycles, the patients should take the morning dose of PLX3397 at the clinical site after the pre-dose PK blood sample is obtained– patients should be instructed not to take the study drug at home prior to these clinic visits. The time of dosing will be recorded in the clinic. The evening dose of PLX3397 should be taken by the patient at home. For **Part 1** on all other visit days and for all **Part 2 and Part 3** visit days, patients may administer the study drug at home and record dosing information in the PLX3397administration diary.

Missed doses of greater than 2 hours after the appropriate dosing time should be skipped and not taken as a double dose at the next dosing time point. For example, a patient who takes their PLX3397 at 8 a.m. and 8 p.m. each day should not take their dose if it has been 14 or more hours since their last dose. This applies to both BID and approved QD dosing.

Patients who vomit their dose should be instructed to NOT make up that dose.

14.1.2 PLX3397 Packaging and Labeling

PLX3397-HCl capsules (100 mg or 200 mg strength of the active free base of PLX3397) are manufactured, packaged, and labeled according to GMP and GCP at the following address:

Catalent Pharma Solutions (formerly Aptuit)
10245 Hickman Mills Drive
Kansas City, MO 64137

14.1.3 PLX3397 Storage and Stability

PLX3397-HCl capsules will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature (between 15–30°C, or 59–86°F).

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

14.1.4 PLX3397 Accountability, Reconciliation, and Return

The investigator is accountable for all test article supplied by the Sponsor. Copies of the completed source dispensing and inventory record(s) will be returned to the Sponsor (or designee) after the Sponsor (or designee) has performed accountability procedures. PLX3397 accountability will also be captured in the EDC throughout the course of the trial.

All PLX3397 capsules must be returned to the contract distribution center with the appropriate form if there is evidence that the product has been tampered with in transit.

Returned and unused PLX3397 capsules may also be destroyed and documented at the investigative site in accordance with GCP. The quantity and dates of destruction of all PLX3397 capsules must be recorded on the PLX3397 accountability log.

14.1.5 PLX3397 Compliance

At each clinic visit, patients will be questioned about their PLX3397compliance. PLX3397 compliance will also be tracked through a patient diary.

14.2 Paclitaxel

Paclitaxel will be administered intravenously over approximately 60 minutes. Paclitaxel will be administered only to patients who have signed and dated an informed consent form. Per Investigator and/or patient preference, 1 dose of paclitaxel may be skipped every four weeks.

15.0 MEASURES TO MINIMIZE/AVOID BIAS

Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The investigator must maintain a patient master log.

16.0 SAFETY EVALUATION

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled and symptom-directed physical examinations, vital sign measurements, 12-lead ECGs (including QTcF intervals), and clinical laboratory test results.

More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator. All AEs will be recorded from the time the patient receives the first dose of study drug up to 28 days after the last dose or prior to start of new anti-tumor therapy, whichever occurs first.

For **Part 3 only**: AE and SAE reporting will commence when the 2-3 core biopsies are obtained during Screening.

16.1 Physical Examination

Physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at Screening and at all time points indicated in the Trial Flow Chart. Photography may be included as part of the physical exam for those patients who consent to the procedure.

16.2 Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position. All patients should be sitting for 3–5 minutes prior to obtaining vital signs.

16.3 Electrocardiograms

Patients should rest in the supine position for at least 5 minutes before each 12-lead ECG recording is started. The ECGs recordings must be performed using a standard, high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements.

For safety monitoring purposes, the ECG must be reviewed, signed and dated promptly 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, PR interval, QRS interval, QT interval, and QTcF interval (corrected QT interval, Frederica's formula). If considered appropriate by the Sponsor, ECGs may be retrospectively analyzed at a central facility.

16.4 Echocardiograms or Multi-gated Acquisition Scans

Either a transthoracic echocardiogram (TTE) or multi-gated acquisition scan (MUGA) will be obtained to evaluate cardiac ejection fraction. Patients should rest in the supine position for at least 5 minutes prior to the evaluation. The Echo or MUGA must be reviewed, signed and dated promptly by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF.

16.5 Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the Trial Flow Chart. Please see Attachment 1 for the specific laboratory tests to be performed.

Patients enrolling in studies with PLX3397 who are also receiving concomitant warfarin should have their anti-coagulation status carefully monitored, especially shortly after initiation of PLX3397, for the potential need to make adjustments in warfarin dosing. In particular, INR

should be obtained just prior to initiation of PLX3397, within 1-2 weeks after initiation, and periodically thereafter. Dose adjustments of warfarin should be made as medically indicated.

17.0 STUDY STOPPING RULES

Part 1:

If ≥2 of 6 patients in Dose Level -1 either experience a DLT or are unable to receive the requisite PLX3397 and paclitaxel doses in the first 28 days due to treatment-related adverse events, the combination will be considered too toxic and the study will be discontinued.

Part 2:

After ~50% of the planned approximately 30 patients (RP2D-treated patients from Part 1 and Part 2) have completed at least 2 treatment cycles, an overall interim safety summary will be reviewed by the Medical Monitor and Principal Investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not warrant continued enrollment, the study will be discontinued.

Part 3:

After ~50% of the approximately planned 30 patients have completed at least 2 treatment cycles, an overall interim safety summary will be reviewed by the Medical Monitor and Principal Investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not warrant continued enrolment, the study will be discontinued.

18.0 BIOMARKER SAMPLES

Blood samples for PD biomarkers will be obtained as noted in the Trial Flow Chart. Samples will be collected, processed and stored according to the study-specific laboratory manual.

Please see Attachment 1 for the specific laboratory tests to be performed on both plasma and tissue samples.

19.0 PHARMACOKINETIC EVALUATION (PART 1 AND PART 3)

19.1 Blood Collection

Approximately 5 mL of blood will be collected via peripheral venipuncture into a lithium heparin tube. This blood sample will be used to measure concentrations of PLX3397 for each PK blood collection, as noted in the Trial Flow Chart. Samples will be collected, processed and stored according to the study-specific laboratory manual.

Blood samples for PK analysis should be collected at the requested time but within a ±10 minute window of the requested time. The exact actual time of collection should be noted in the source documents and eCRFs.

19.2 Bioanalytical Methodology

The plasma samples will be analyzed for PLX3397 by using a validated method (high performance liquid chromatography (HPLC) with tandem quadruple mass spectrometric detection) of appropriate specificity and sensitivity.

20.0 STATISTICAL ANALYSIS

20.1 Safety Analysis

All patients in all cohorts who receive study medication will be considered evaluable for safety regardless of their duration of treatment.

The objective of the dose escalation is to determine a dose of PLX3397 (plus paclitaxel) for which the rate of DLTs is less than 33%. Safety variables to be analyzed are AEs, laboratory test results (hematology, clinical chemistry and urinalysis), ECG, and vital signs. Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 7.1 or higher. All AEs will be summarized for each dose group according to the system organ class and preferred term within the organ class. Adverse events will be tallied for overall frequency (number and percentage of patients), worst reported severity, and relationship to study drug for each preferred term per patient. 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. In addition, all events meeting the criteria of a DLT will be tabulated as a separate listing by patient and dose group. Laboratory variables will be summarized using mean change in value from baseline to scheduled time points for each dose level group and 95% confidence interval. Laboratory values will also be categorized according to their CTCAE (version 4) toxicity grade and tabulated by worst on-study toxicity grade and dose level group. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first study treatment dose. Concomitant medications will also be summarized.

20.2 Efficacy Analysis

All patients with measurable disease by RECIST version 1.1 criteria (see Attachment 2) at Baseline who complete at least one post-baseline radiographic assessment or discontinue study medication early due to disease progression will be considered evaluable for efficacy.

Response to treatment according to the RECIST criteria will be reported via descriptive statistics by dose level. The absolute and percent change from baseline for the extent of disease (sum of

the longest diameters) will be summarized at each scheduled evaluation using descriptive statistics including mean, standard deviation, minimum and maximum values.

All patients who are eligible for efficacy analyses will be evaluable for progression–free survival, regardless of the presence or absence of measurable disease. Progression-free survival will be calculated for each patient and shown for all patients on a Kaplan-Meier plot. Progression-free survival is defined as the number of days from the first day of treatment to the date of the first documented disease progression or date of death, whichever occurs first.

For each patient with a response to therapy, duration of response will be calculated. The duration of response is defined as number of days from the date of initial response (confirmed at least 28 days later) to the date of first documented disease progression or death, whichever occurs first. If the information is available, the pre-study stability of disease will also be recorded to assist the interpretation of the on-treatment progression-free survival.

In the event no disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, progression-free survival and duration of response will be censored at the date of last evaluable tumor assessments. Exploratory analyses may be conducted to evaluate possible relationships between antitumor activity, pharmacodynamic markers, and drug exposure levels.

20.3 Sample Size and Power

The primary objective of the study is to assess the safety of combination PLX3397+Paclitaxel therapy in a limited number of patients with solid tumors. The number of patients is not based on statistical power considerations.

Part 1. Three-to-six patients will be accrued per dose level in order to insure the safety and tolerability. The probabilities of detecting DLTs in this study are shown in Table 4 and Table 5.

Table 4: Probabilities of Detecting DLTs (3 Patients)

Number DLTs in a Cohort of 3 Patients	Incidence of DLTs in Patient Population				
	0.10	0.20	0.30	0.40	0.50
0[a]	0.729	0.512	0.343	0.216	0.125
1[b]	0.243	0.384	0.441	0.432	0.375
2 or more[c]	0.028	0.104	0.216	0.352	0.500

[a] Number of DLTs leads to advancing to the next cohort.

[b] Number of DLTs leading to enrolling an additional 3 patients in the Cohort.

[c] Number of DLTs leading to stopping the study and defining the MTD.

Table 5: Probabilities of Detecting DLTs (6 Patients)

Number DLTs in a Cohort of 3 Patients	Incidence of DLTs in Patient Population				
	0.10	0.20	0.30	0.40	0.50
0	NA	NA	NA	NA	NA
1[a]	0.177	0.197	0.151	0.093	0.047
2 or more[b]	0.066	0.187	0.290	0.339	0.328

[a] Number of DLTs leading to advancing to the next cohort [Prob (1 in first 3 and 0 in second 3)].

[b] Number of DLTs leading to stopping the study and defining the MTD [Prob (1 in first 3 and 1 in second 3) + Prob (1 in first 3 and 2 in second 3)].

20.4 Pharmacokinetic Analysis (Part 1 and Part 3)

A non-compartmental method of analysis will be used to analyze the plasma concentrations of PLX3397 C_{max} at steady state (i.e., C1D15) and the time to attain the C_{max} (T_{max}) will be determined directly from the observed data. A partial AUC (AUC_{0-4}) will be calculated on Day 15 in Cycle 1.

20.5 Pharmacodynamic Analysis

No formal statistical analysis of pharmacodynamic endpoints will be performed. Pharmacodynamic data from each assay will be listed by dose. Possible relationships between PK and pharmacodynamic variables will be explored, as appropriate. Any biological activity will be described.

21.0 PRECAUTIONS

Although major adverse events are not anticipated, the investigator must proceed with utmost caution. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected reaction. Patients must be carefully selected and closely monitored.

For a complete description of preclinical and clinical studies of PLX3397, please refer to the PLX3397 Investigator's Brochure. For a complete description of paclitaxel, please refer to the product label's indications and usage instructions.

22.0 ADVERSE EVENTS

For safety information on PLX3397, refer to the most recent version of the Investigator's Brochure. For safety information on paclitaxel, refer to the product label's indications and usage.

22.1 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article in a clinical study. The event does not need to be causally related to the test article. 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 test article, whether accidental or intentional.
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a test article.
- An AE that has been associated with the discontinuation of the use of a test article.

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

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

A **serious adverse event** is an AE that:

- Results in death (NOTE: death is an outcome, not an event)
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 necessarily 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.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, which might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a serious adverse event (SAE).In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery).This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls in the same category.

In addition, hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE. Visits to the Emergency Room that do not result in hospital admission are not considered hospitalizations.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Relatedness to study medication will be graded as either "probably", "possibly", or "not related", as follows:

Probably – The adverse event:

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the drug
- Cannot be reasonably explained by the known characteristics of the patient's clinical state

Possibly – The adverse event:

- Follows a reasonable temporal sequence from drug administration
- Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient

Not Related – The adverse event:

- Does not follow a reasonable sequence from drug administration
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e., related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information: certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- A case involving a pregnancy exposure to a test article, unless the product is indicated for use during pregnancy e.g., prenatal vitamins. Information about use in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. If a pregnancy is confirmed, test article must be discontinued immediately. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. Pregnancies occurring up to 6 months after completion of the study treatment must also be reported to the investigator.
- Overdose (e.g., a dose higher than that indicated in the protocol) with or without an AE.
- Abuse (e.g., use for nonclinical reasons) with or without an AE.
- Inadvertent or accidental exposure with or without an AE.
- Device malfunction with or without an AE.

22.2 Recording and Reporting

A patient's AE or SAE can occur from the time the patient receives the first dose of study drug up to 28 days after the last dose and prior to starting another therapy. For **Part 3 only**, AE and SAE reporting will commence when the 2-3 core biopsies are obtained during Screening.

The investigator must follow-up on all drug-related AEs, SAEs, and other reportable information until the events have subsided, returned to baseline, the patient has initiated any other anticancer treatment, or in case of permanent impairment, until the condition stabilizes.

All AE and SAEs must be recorded on source documents and collected in EDC.

AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the patient. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the patients must be reported promptly to the IRB/IEC.

22.3 Serious Adverse Event Reporting

All SAEs, other reportable information, and follow-up information must be reported within 24 hours of learning of the event by completing the SAE eCRF in the electronic data capture (EDC) system. As a back-up, the site may fax a completed serious adverse event form to the fax number indicated in the Emergency Contacts section and confirming by phone or e-mail that the fax was received. Plexxikon (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Plexxikon will make a determination as to whether the criteria for expedited reporting have been met.

Plexxikon (or designee) is responsible for reporting relevant SAEs to the relevant regulatory authorities and participating investigators, in accordance with FDA regulations *21 CFR 312.32, ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC)*, and/or local regulatory requirements. To meet this requirement, Plexxikon (or designee) may request additional information from the sites, including but not limited to, hospitalization records. Any requests for such information should be addressed in a timely manner.

Reporting of SAEs by the investigator to the Institutional Review Board (IRB) or Ethics Committee (EC) will be done in accordance with the standard operation procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

23.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the investigator suspends or terminates the study, the investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The investigator will also return all test article, containers, and other study materials to the Sponsor's contract distribution center, or destroy the materials at the investigative site. Upon study completion, the investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. For IND studies, the investigator must submit a written report to the Sponsor and the IRB/IEC within 3 months after the completion or termination of the study.

24.0 INFORMED CONSENT

The investigator will provide for the protection of the patients by following all applicable regulations. These regulations are available upon request from the Sponsor. The informed consent form used during the informed consent process must be reviewed by the Sponsor and approved by the IRB/IEC.

Before any procedures specified in the protocol are performed*, a patient must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB/IEC approved informed consent form.

* = Data from standard-of-care procedures performed prior to informed consent may be used for screening purposes if the procedure occurred within the protocol-specified timeframe.

25.0 PROTOCOL AMENDMENTS

Any significant change in the study requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and Sponsor approval except when necessary to eliminate apparent immediate hazards to the patients. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved following the same process as the original protocol.

26.0 QUALITY CONTROL AND ASSURANCE

The Sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, Sponsor personnel and the investigator

review the protocol, the investigator's brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

27.0 DIRECT ACCESS, DATA HANDLING, AND RECORD KEEPING

27.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All study-related information will be recorded on source documents. All required data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

All study-related laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patients' study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Patient personal health information that is accessed for this study will not be reused or disclosed to any other person or entity, or for other research.

27.2 Sponsor

The data will be checked for completeness and correctness in real-time online.

Data are checked as they are entered into the electronic data capture system (EDC). Off-line checks will also be run to assess the need for additional data review. Discrepancy reports will be generated and transferred to the study center for resolution by the investigator or his/her designee.

28.0 PRE-STUDY DOCUMENTATION

The investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed form 1572.
- All applicable country-specific regulatory forms.

- Current signed and dated curricula vitae for the investigator, sub investigators, and other individuals having significant investigator responsibility who are listed on the Form 1572 or equivalent, or the clinical study information form.
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved informed consent document to be used.
- Where applicable, a list of the IRB/IEC members or a FWA/DHHS number.
- Copy of the protocol sign-off page signed by the investigator.
- Copy of the current medical license of the principal Investigator, any sub investigators and any other individuals having significant responsibility as listed in the 1572.
- Fully executed Clinical Trial Agreement.
- Where applicable, a financial disclosure form for the Principal Investigator and any other persons listed in the 1572.
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the 1572 and the laboratory director's curricula vitae and active medical license. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The Sponsor must be notified if normal values or units of measurement change.

29.0 RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (I) 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug or (ii) such longer period as required by applicable global regulatory requirements .At the end of such period, the investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

30.0 REFERENCES

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ATTACHMENT 1: LABORATORY TESTS

HEMATOLOGY (Peripheral Blood Sample)

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

SERUM CHEMISTRY (Peripheral Blood Sample)

- Sodium
- Potassium
- Chloride
- CO_2
- Magnesium
- Calcium
- 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)
- Creatine kinase (CPK)

* = Fasting Glucose (8–10 hour fast) is recommended, but not required

Pregnancy test (urineβ-HCG): Women of child-bearing potential

Part 1, Part 2, and Part 3:

Blood Response Biomarkers (samples):

- CSF-1
- CD14/CD16 positive monocytes

(Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, a definitive list of analyses remains to be determined.)

Part 3:

Cancer tissue biomarkers will include:

- IHC for CD68, CD8, PD-L1, and additional markers of macrophage and T-cell presence and function

- RNA expression analysis for an exploratory panel of tumor microenvironment markers
- Staining of cells of the tumor microenvironment. Panels of IHC markers specific for macrophages, T-cells, and other immune and inflammatory cells will be employed, for semi-quantitative changes in cell number, location within the tumor, and degree of activation.

Blood biomarkers will include:

- CA-125 sampling requirements: 2 pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of Cycle 1 Day 1; subsequent samples on the first day of each cycle starting with Cycle 2 Day 1 and End-of-Study Visit.
- Plasma CSF-1 and additional markers of treatment effect
- Whole blood CD14/CD16 monocyte subset by FACS analysis
- Whole blood MDSC by FACS analysis

ATTACHMENT 2: RECIST CRITERIA VERSION 1.1

Measurability of Tumor at Baseline

Definitions

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

Measurable tumor lesions

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

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable tumor lesions

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

Special considerations regarding lesion measurability

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

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Lesions with prior local treatment:

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

Specifications by methods of measurements

Measurement of lesions

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

Method of assessment

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

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

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

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

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in this Attachment 2). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

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

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

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to **reproducible repeated measurements**. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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

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

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

Response criteria

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

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

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

Target lesions that become 'too small to measure': while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

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

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

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

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

Evaluation of non-target lesions

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

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

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

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

Special notes on assessment of progression of non-target disease

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

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

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

New lesions

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

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI

ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

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

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

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

Evaluation of best overall response

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

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 6 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 7 is to be used.

Missing assessments and not-evaluable designation

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

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

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

Best overall response: all time points

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

Table 6: Time Point Response: Patients with Targets (± Non-Target) Disease

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

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

Table 7: Time Point Response: Patients with Non-Target Disease Only

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

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

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

Table 8: Best Overall Response When Confirmation of CR and PR Required

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

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

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

Special notes on response assessment

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

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an

objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 6, Table 7, and Table 8.

Conditions that define 'early progression, early death and non-evaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

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

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

ATTACHMENT 3: STRONG CYP3A4 INHIBITORS AND INDUCERS

Strong Inhibitors	Strong Inducers
Protease inhibitors • Ritonavir • Indinavir • Nelfinavir Macrolide antibiotics • Erythromycin • Telithromycin • Clarithromycin Azole antifungals • Fluconazole • Ketoconazole • Itraconazole Chloramphenicol (antibiotic) Nefazodone (antidepressant) Bergamottin (constituent of grapefruit juice) Aprepitant (antiemetic) Verapamil (calcium channel blocker)	Anticonvulsants, mood stabilizers • Phenytoin • Carbamazepine • Oxcarbazepine Non-nucleoside reverse transcriptase inhibitors • Efavirenz • Nevirapine • Etravirine Phenobarbital (barbiturate) Rifampicin (bactericidal) Modafinil (stimulant) Hyperforin (constituent of St Johns Wort) Cyproterone (antiandrogen, progestin)

ATTACHMENT 4: METHODS OF BIRTH CONTROL

All WOCBP and sexually active men must agree to use acceptable methods of contraception throughout the course of their participation in this study and for at least 3 months after their last dose of study drug. WOCBP must agree to use **two** forms of contraception. Sexually active male participants must agree to use a physical barrier method (male latex rubber condom with or without spermicide).

Table 9: List of Permissible Contraceptive Methods

Method	Women Experiencing Unintended Pregnancy Within the First Year of Use (%)	
	Typical Use[1]	Perfect Use[2]
Spermicides[3]	29	18
Condom[4]	-	-
Male	15	2
Combined pill and progestin-only pill	8	0.3
Evra Patch	8	0.3
NuvaRing	8	0.3
Depo-Provera	3	0.3
Intrauterine device (IUD)	-	-
ParaGard (copper T)	0.8	0.6
Mirena (LNG-IUS)	0.2	0.2
Implanon	0.05	0.05
Female Sterilization	0.5	0.5
Male Sterilization	0.15	0.10

Source: Trussell J. Contraceptive Efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W Jr., Stewart FH, Kowal D, editors. Contraceptive Technology. 19th ed. New York, NY: Ardent Media, Inc.; 2007.

1. Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides, withdrawal, periodic abstinence, the diaphragm, the male condom, the pill, and Depo-Provera are taken from the 1995 National Survey of Family Growth corrected for underreporting of abortion; see the text for the derivation of estimates for the other methods.
2. Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
3. Spermicides are only permitted when used in combination with a male physical barrier method
4. Without spermicides.

ATTACHMENT 5: AMENDMENT 1 SUMMARY OF CHANGES

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes.

Section(s)	Original Protocol	Amendment 1	Rationale
Major Modifications			
Synopsis and Section 10.1	12. Adequate bone marrow reserve: **ANC ≥1000/mm^3**, platelets ≥100,000/mm^3	12. Adequate bone marrow reserve: **ANC ≥1500/mm^3**, platelets ≥100,000/mm^3	Modification to ensure patients have adequate bone marrow reserves to receive paclitaxel
Synopsis and Section 10.1	14. Adequate hepatic function: AST and ALT <2.5x ULN; Total and Direct Bilirubin <1.5x **ULN.** However, in the presence of liver metastases, AST and ALT must be <5x ULN **and Total and Direct Bilirubin must be <3x ULN.**	14. Adequate hepatic function: AST and ALT <2.5x ULN. Total and Direct Bilirubin <1.5x ULN. However, in the presence of liver metastases, AST and ALT must be <5x ULN.	Modification to ensure patients have adequate hepatic function prior to enrollment into the trial. Patients with liver metastases must meet the same Total and Direct Bilirubin levels as patients without liver tumor involvement.
Synopsis and Section 10.1	15. Cardiac ejection fraction ≥50%, and **QTcF <450 ms** on ECG at Baseline	15. Cardiac ejection fraction ≥50%, **and QTcF <450ms (males) or <470 ms (females)** on ECG at Baseline	Modification to accommodate female normal range for QTcF
Synopsis and Sections 13.2 and 13.5		A whole blood sample for circulating CD14/CD16 positive monocyte analysis will be obtained pre dose [on C1D1 and C1D15	Addition to gather additional pharmacodynamic data PLX3397 + paclitaxel combination
Synopsis and Section 13.12	[Non-hematologic DLTs-exemptions] • Grade 3 fatigue that resolves within 14 days, with or without medical intervention or prophylaxis	[Non-hematologic DLTs-exemptions] • Grade 3 fatigue that **resolves to ≤Grade 2** within 14 days	Addition of resolution to Grade 2 for more specificity in the Grade 3 fatigue DLT exemption definition.

Section(s)	Original Protocol	Amendment 1	Rationale
Synopsis and Section 13.12		[Non-hematologic DLTs] • **Grade 3 peripheral neuropathy in patients with baseline ≥Grade 1 peripheral neuropathy or a history of chemotherapy-associated peripheral neuropathy** • **Grade 3 myalgia or arthralgia in patients with baseline ≥Grade 1 myalgia or arthralgia** • **Grades 3 rash for which symptoms are easily managed with supportive care and there is no evidence of superinfection or limitation of self-care ADLs.**	Addition of Grade 3 peripheral neuropathy in patients will Grade 1 symptoms as a DLT exemption because peripheral neuropathy is a common toxicity associated with taxanes and other chemotherapies. Acute symptoms or worsening of peripheral neuropathy with paclitaxel in this patient population is expected. Addition of Grade 3 myalgia or arthragia because these are common toxicities associated with paclitaxel treatment and expected in this population. Addition of Grade 3 manageable rash because this is a common toxicity associated with paclitaxel treatment and expected in this population.
Synopsis and Section 13.12	**A treatment delay of greater than 7 days for PLX3397 or missing more than 1 out of the 4 weekly doses of paclitaxel in the first cycle due to toxicity that is not related to cancer worsening or intercurrent illness will be considered a DLT.**		Removed as this is covered by the DLT definitions. Patients who miss doses of either PLX3397 or paclitaxel during Cycle 1 for reasons other than a DLT will be replaced.

Section(s)	Original Protocol	Amendment 1	Rationale
Section 12.0	Filgrastim growth factor support is encouraged for ANC <1500/mm^3 and may be used at the discretion of the treating physician in order to maintain adequate blood counts **EXCEPT during the first cycle.** Filgrastim is not permitted within 24 hours prior to or following any paclitaxel infusion. Pegfilgrastim (Neulasta) is not permitted in this study.	Filgrastim growth factor support is encouraged for ANC <1500/mm^3 and may be used at the discretion of the **Principal Investigator in consultation with the Medical Monitor. Growth factors may be administered throughout the study, including during Cycle 1, in order to maintain adequate blood counts. For patients whose ANC is between 1500–2000 cells/mm^3, Filgrastim may be administered from days 2–5 (total of 4 days) after the most recent paclitaxel infusion.** Filgrastim is not permitted within 24 hours prior to or following any paclitaxel infusion. Pegfilgrastim (Neulasta) is not permitted in this study.	Modification. Growth factor support is regularly used in routine practice to help patients achieve adequate neutrophil counts in order to receive paclitaxel. This modification was made in order to make this protocol consistent with the standard-of-care for weekly paclitaxel.
Synopsis, Sections 9.2 and 13.15	One dose of paclitaxel may be skipped **every [three/four] weeks** for subsequent cycles (i.e., Cycle 2+) per Investigator discretion and/or patient preference.	One dose of paclitaxel may be skipped **per Cycle** for subsequent cycles (i.e., Cycle 2+) per Investigator discretion and/or patient preference**. In general, two consecutive doses of paclitaxel should not be skipped.**	Modification and clarification. The original protocol was inconsistent between stating every three weeks or every four weeks. The modification was added to clarify the permitted frequency for skipping a paclitaxel dose.
Section 7.6	The ongoing Phase 1 dose escalation study PLX108-01…[ ]..As of **June 2011**, a total of **41** patients have been treated with PLX3397 PO…[ ]…the mean accumulation ratio compared to Day 1 values is approximately **1.6**. In general, there is increasing exposure with increasing dose…[ ]… The most common AEs have been **nausea and fatigue**.	The ongoing Phase 1 dose escalation study PLX108-01…[ ]…As of **June 2012**, a total of **62** patients have been treated with PLX3397 PO**, including 41 patients in the dose escalation cohorts and 21 patients in the Extension cohorts**…[ ]… the mean accumulation ratio compared to Day 1 values is approximately **2:1**. In general**, there is good dose proportionality,** with increasing exposure with increasing dose…[ ]… The most common AEs have been **fatigue, decreased appetite and nausea**.	General updates based on new data

Section(s)	Original Protocol	Amendment 1	Rationale
Section 12.0		**Prophylaxis or medical management for nausea and vomiting with antiemetics is encouraged, particularly in patients with a history of nausea or vomiting with prior taxane therapy.**	Addition to provide guidance for preventing and managing nausea and vomiting.
Section 13.14	PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 only if a patient experiences a DLT. If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be permitted at the discretion of the Investigator and in consultation with the Medical Monitor. After C1D28, dose reductions or interruptions for adverse events may take place at any time.	PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 only if a patient experiences a DLT**. PLX3397 interruptions during Cycle 1 are also permitted for Grade 3 vomiting that persists despite optimal supportive care.** If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be permitted at the discretion of the Investigator and in consultation with the Medical Monitor. After C1D28, dose reductions or interruptions for adverse events may take place at any time.	Addition to clarify patient management of Grade 3 emesis in Cycle 1.
Section 13.14		**For Grade 3 emesis that persists despite optimal supportive care, PLX3397 doses should be held until resolution to Grade 2 or less.**	Addition for clarification on the management of emesis
Section 13.14		**For cases of Grade 3 symptomatic rash that persists despite medical intervention, PLX3397 doses should be held until resolution to Grade 2 or less. Upon reintroduction of PLX3397, the dose level should be reduced by 200 mg/day.**	Addition for clarification on the management of rash
Section 13.16	When a patient discontinues or is withdrawn, the investigator will notify the Sponsor (or designee) and should perform the procedures indicated in the End of Rx column in the study flow chart within **30** days after discontinuation of study drug and prior to initiation of any therapy.	When a patient discontinues or is withdrawn, the investigator will notify the Sponsor (or designee) and should perform the procedures indicated in the End of Rx column in the study flow chart within **28** days after discontinuation of study drug and prior to initiation of any therapy.	Modification for consistency with previous sections

Section(s)	Original Protocol	Amendment 1	Rationale
Section 14.1.2	Aptuit 10245 Hickman Mills Drive Kansas City, MO 64137	Catalent Pharma Solutions (formerly Aptuit) 10245 Hickman Mills Drive Kansas City, MO 64137	Update
Section 21.3	All SAEs, other reportable information, and follow-up information must be reported within 24 hours of learning of the event by completing the SAE eCRF.	All SAEs, other reportable information, and follow-up information must be reported within 24 hours of learning of the event by completing the SAE eCRF **in TEMPO**.	Clarification
Table 3: Dose Modification Guidelines for PLX3397	[Hematological toxicity dose reductions occurred in 300 mg/day increments]	[Hematological toxicity dose reductions changed to occur in 200 mg/day increments]	Modification for consistency with non-hematological toxicity dose reduction increments

ATTACHMENT 6: AMENDMENT 2 SUMMARY OF CHANGES

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes.

Section(s)	Original Protocol	Amendment 2	Rationale
Major Modifications			
Synopsis and Section 8.0	The primary objective of this Phase 1b study is to establish the dose limiting toxicities (DLTs) **and maximum tolerated dose (MTD)** of PLX3397 when given in combination with weekly standard dose paclitaxel in patients with advanced solid tumors.	The primary objective of this Phase 1b study is to establish the dose limiting toxicities (DLTs) and **recommended Phase 2 dose (R2PD)** of PLX3397 when given in combination with weekly standard dose paclitaxel in patients with advanced solid tumors.	Modification to permit the selection of the RP2D based on either PK data or reaching an MTD. If absorption and systemic exposure of PLX3397 reaches a plateau prior to establishment of an MTD, it would not be necessary to continue escalating PLX3397 dosage.
Synopsis	This is a nonrandomized, open-label phase 1b study employing a standard 3+3 dose escalation design to determine the **MTD** of PLX3397, a novel inhibitor of the CSF-1 receptor (Fms), when administered in combination with paclitaxel in patients with advanced solid tumors.	This is a nonrandomized, open-label phase 1b study employing a standard 3+3 dose escalation design to determine the **RP2D** of PLX3397, a novel inhibitor of the CSF-1 receptor (Fms), when administered in combination with paclitaxel in patients with advanced solid tumors.	Modification to permit the selection of the RP2D based on either PK data or reaching an MTD. If absorption and systemic exposure of PLX3397 reaches a plateau prior to establishment of an MTD, it would not be necessary to continue escalating PLX3397 dosage.
Synopsis	PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. **The planned cohorts are Cohort 1: 600 mg/day, Cohort 2: 800 mg/day and Cohort 3: 1000 mg/day**	PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. **The starting dose of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%.**	Modification to permit escalation of PLX3397 beyond 1000 mg/day based on safety and tolerability data.

Section(s)	Original Protocol	Amendment 2	Rationale
Section 9.1	Protocol PLX108-07 is a Phase 1b open-label, sequential dose escalation trial of PLX3397 plus paclitaxel. The study employs a traditional 3+3 design. Treatment with PLX3397 will consist of continuous oral administration and enrollment will begin at the 600 mg/day dose level for 28 days. Paclitaxel will be administered once weekly (±48 hours).	Protocol PLX108-07 is a Phase 1b open-label, sequential dose escalation trial of PLX3397 plus paclitaxel. The study employs a traditional 3+3 design. Treatment with PLX3397 will consist of continuous oral administration and enrollment will begin at the 600 mg/day dose level for 28 days. Paclitaxel will be administered once weekly (±48 hours). **The planned schedule for PLX3397 dose escalations is shown in Table 2. For doses higher than 1000 mg/day, the dose escalation increment may be adjusted based on the observed toxicity and systemic exposure at the previous dose level. However, the maximum dosing increment will be 50%.**	Modification to permit escalation of PLX3397 beyond 1000 mg/day based on safety and tolerability data.
Section 9.1 Table 2		[PLX3397 Dose Levels 3 (1200 mg/day, 4 (1600 mg/day) and 5 2000 mg/day) added to Dose Escalation Schedule]	Modification to provide dosing plan and instructions for PLX3397 dose levels above 1000 mg/day
Synopsis	The total number of patients to be enrolled will depend on the number of cohorts and whether a cohort requires 3 or 6 patients	The total number of patients to be enrolled will depend on the number of cohorts, whether a cohort requires 3 or 6 patients **and whether patients who are not evaluable for DLTs need to be replaced.**	Updated to take into account the enrollment of additional patients in a given cohort to replace patients who are not evaluable for DLTs

Section(s)	Original Protocol	Amendment 2	Rationale
Section 9.2	A fixed dose of paclitaxel, 80 mg/m^2, will be administered intravenously, once weekly (±48 hours). Patients must receive at least 3 of 4 paclitaxel doses during the DLT period (i.e., Cycle 1). One dose of paclitaxel may be skipped per Cycle for subsequent cycles (i.e., Cycle 2+) per Investigator discretion and/or patient preference. In general, two consecutive doses of paclitaxel should not be skipped.	A fixed dose **level** of paclitaxel, 80 mg/m^2, will be administered intravenously, once weekly (±48 hours). Patients must receive at least 3 of 4 paclitaxel doses during the DLT period (i.e., Cycle 1) **in order to be considered evaluable for DLT, unless doses are missed due to a DLT.** One dose of paclitaxel may be skipped per Cycle for subsequent cycles (i.e., Cycle 2+) per Investigator discretion and/or patient preference. In general, two consecutive doses of paclitaxel should not be skipped.	General clarifications for required dosing in Cycle 1
Section 9.2	The PLX3397 + paclitaxel combination will be offered to each patient as long as both the patient and Investigator agree that it continues to be well tolerated and the patient is clinically benefitting	[paragraph deleted]	Redundant with statement in Section 9.6
Section 14.1.1	PLX3397 should be taken orally with 240 mL (8 oz) of **room temperature** water in the fasting state.	PLX3397 should be taken orally with 240 mL (8 oz) of water in the fasting state.	Modification of instructions. Water temperature is not recorded and is not necessary for the proper administration of PLX3397
Section 14.1.1	Missed doses of greater **than 2 hours before or after the appropriate dosing** time should be skipped and not taken as a double dose at the next dosing timepoint. For example, a patient who takes their PLX3397 at 8 a m. and 8 p.m. each day should not take their dose **if they are outside of the ± 2 hr window period.** This applies to both BID and approved QD dosing.	Missed doses of greater than **2 hours after the appropriate dosing time** should be skipped and not taken as a double dose at the next dosing timepoint. For example, a patient who takes their PLX3397 at 8 a m. and 8 p m. each day should not take their dose if **it has been 14 or more hours since their last dose.** This applies to both BID and approved QD dosing.	Modification of instructions. A missed dose would not occur prior to the scheduled dosing time.

ATTACHMENT 7: AMENDMENT 3 SUMMARY OF CHANGES

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes.

Section(s)	Original Protocol	Amendment 3	Rationale
Cover page	[redacted] Phone: [redacted]	[redacted] **Phone:** [redacted]	Update contact information
Section 4.1 Emergency Contacts	Medical Monitor: Name: [redacted] Phone: [redacted] Email: [redacted]	**Medical Monitor:** **Name:** [redacted] **Phone:** [redacted]	Update contact information
Section 4.2 Additional Contacts	[redacted]	[redacted]	Update contact information
Synopsis, Trial Flow Chart and Section 13.11 End of Treatment	End of Treatment	End of ~~Treatment~~ **Study**	Clarification that 'End of Treatment' is the last day study drug is taken, while 'End of Study' is the last visit following study drug discontinuation and before initiation of new antitumor therapy.
	End of Rx	End of ~~Rx~~ **Study**	
	End of Treatment All patients discontinuing study treatment for any reason should return to the clinic within 28 days following their last dose of the study drug combination or prior to receiving new antitumor therapy....	End of ~~Treatment~~ **Study** All patients discontinuing study treatment for any reason should return to the clinic within 28 days following their last dose of the study drug combination ~~**or**~~ **and** prior to receiving new antitumor therapy....	
Section 13.16 Discontinuation of Treatment and Withdrawal of Patients	When a patient discontinues or is withdrawn, the investigatorr will notify the Sponsor (or designee) and should perform the procedures indicated in the End of Rx column in the study flow chart within 28 days after discontinuation of study drug and prior to initiation of any therapy.	When a patient discontinues or is withdrawn, the investigator will notify the Sponsor (or designee) and should perform the procedures indicated in the End of Rx **Study** column in the study flow chart within 28 days after discontinuation of study drug and prior to initiation of any new **antitumor** therapy.	Modification for consistency with previous sections

Section(s)	Original Protocol	Amendment 3	Rationale
Trial Flow Chart	Superscript errors: Paclitaxel Administration[4] Vital Signs[9] 12-Lead ECG[10] Chemistry[13] Hematology[11] Urine Pregnancy Test[12] Adverse Events[8]	Superscript Corrections: Paclitaxel Administration[4,6] Vital Signs[10] 12-lead ECG[11] Chemistry[14] Hematology[12] Urine Pregnancy Test[13] Adverse Events[9]	Correction of numbering errors
	Plasma for PK: Day 1: X[6] Cycle 1 Day 15: X[7] Cycle 2 Day 1: X[14] Plasma for PD biomarkers: Day 1: X[14] Cycle 2 Day 1: X[14]	Plasma for PK: Day 1: X[7] Cycle 1 Day 15: X[8] Cycle 2 Day 1: X[7] Plasma for PD biomarkers: Day 1: X[15] Cycle 2 Day 1: X[15]	
Trial Flow Chart	Explanation of Superscript #2: The a m. dose of PLX3397 may be taken at home, prior to the clinic visit on all clinic visit days except on C1D1 (Baseline) and C1D15. On those two study days, the morning dose of PLX3397 will be administered in the clinic after obtaining a pre-dose blood sample for PK analysis.	Explanation of Superscript #2: The a.m. dose of PLX3397 may be taken at home, prior to the clinic visit on all clinic visit days except on C1D1 (Baseline) ~~and~~ C1D15**, and C2**+**D1**. On those ~~two~~ study days, the morning dose of PLX3397 will be administered in the clinic after obtaining a pre-dose blood sample for PK analysis.	Modification for consistency with protocol section 13.8
Section 9.1, Table 2	Level 5 PLX3397 BID Dose (800 mg PO BID)	Level 5 PLX3397 BID Dose (**1000** ~~800~~ mg PO BID)	Correction of typographical error.

ATTACHMENT 8: AMENDMENT 4 SUMMARY OF CHANGES

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
6.0 SYNOPSIS: Study Objective(s)	*Amendment 3 does not contain Part 2.*	**This trial is designed as a two-part study: Part 1 (Phase 1b), to explore the safety of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D; and, Part 2, to determine the efficacy and safety of the PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors.**	Once the RP2D has been determined, the efficacy and safety of the PLX3397 will be determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.
6.0 SYNOPSIS: Study Design	This is a nonrandomized, open-label.... *Amendment 3 does not contain Part 2.*	**Part 1:** This is a non-randomized, open label…. **Part 2:** **This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 15 patients (including all RP2D-treated patients from Part 1 and Part 2). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.**	Once the RP2D has been determined, the efficacy and safety of the PLX3397 will be determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.
6.0 SYNOPSIS: Number of Patients/Sites	Enrollment is planned to include... *Amendment 3 does not contain Part 2.*	**Part 1:** Enrollment is planned to include **Part 2:** **Enrollment is planned to include approximately 15 patients (including RP2D-treated patients from Part 1 and Part 2) recruited from 3 sites.**	Once the RP2D has been determined, the efficacy and safety of the PLX3397 will be determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
6.0 SYNOPSIS: Number of Patients/Sites (continued)	Patients who do not receive the requisite PLX3397 and/or paclitaxel doses....	**Part 1 and Part 2:** Patients who do not receive the requisite PLX3397 and/or paclitaxel doses….	This statement applies to both Parts 1 and 2.
6.0 SYNOPSIS: Study Treatments	PLX3397 will be administered orally, twice daily.... *Amendment 3 does not contain Part 2.*	**Part 1:** PLX3397 will be administered orally, twice daily…. **Part 2:** **PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. The dose of PLX3397 will be the RP2D. There will be no dose escalation.** **Part 1 and Part 2:** **Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle.**	Once the RP2D has been determined, the efficacy and safety of the PLX3397 will be determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.
6.0 SYNOPSIS: Study Procedures	After providing informed consent, patients will undergo screening for eligibility to participate in the study. Screening will start within 28 days prior to the first study treatment dose. The physical exam and laboratory values should be obtained within 14 days prior to dosing. Evaluations performed as part of standard-of-care and prior to informed consent may be used if they occur within the protocol-specified timeframe. All female patients of child-bearing potential must have a negative urine pregnancy test within 14 days of C1D1.	~~After providing informed consent, patients will undergo screening for eligibility to participate in the study. Screening will start within 28 days prior to the first study treatment dose. The physical exam and laboratory values should be obtained within 14 days prior to dosing. Evaluations performed as part of standard-of-care and prior to informed consent may be used if they occur within the protocol-specified timeframe.~~ ~~All female patients of child-bearing potential must have a negative urine pregnancy test within 14 days of C1D1.~~	Paragraphs moved under new Part 1 and 2.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
6.0 SYNOPSIS: Study Procedures (continued)	This study will employ a traditional 3+3 Phase 1 design, with escalating dosing cohorts of PLX3397 and a fixed dose level of paclitaxel. Each treatment cycle will be 28 days.	**Part 1: This non-randomized, open-label** study will employ a traditional 3+3 Phase 1 design, with escalating dosing cohorts of PLX3397 and a fixed dose level of paclitaxel. Each treatment cycle will be 28 days. **Dosing of PLX3397 will commence at the 600 mg/day dose level. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). On non-PK/PD paclitaxel administration days, the morning dose of PLX3397 may be administered at home, prior to paclitaxel administration. The starting dose level of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%. All patients at a given dose level will be followed on treatment for at least 4 weeks before accrual to the next cohort can begin. There will be no intra-patient dose escalation permitted. PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 only if a patient experiences a DLT.** **PLX3397 interruptions during Cycle 1 are also permitted for Grade 3 vomiting that persists despite optimal supportive care. If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be permitted at the discretion of the Investigator and in consultation with the Medical Monitor. After C1D28, dose reductions or interruptions for adverse events may take place at any time.**	Clarify that this is nonrandomized, open label and elaboration on Part 1 procedures.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
6.0 SYNOPSIS: Study Procedures (continued)	*Amendment 3 does not contain Part 2.*	**Part 2:** **This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 15 patients (RP2D-treated patients from Part 1 and Part 2). Each treatment cycle will be 28 days.** **Dosing of PLX3397 will commence at the RP2D. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). There will be no intra-patient dose escalation permitted. PLX3397 dose reductions or interruptions for adverse events may take place at any time.**	Added Part 2 study procedures for clarity.
6.0 SYNOPSIS: Study Procedures (continued)	Patients will receive study treatment as long as it is well tolerated and both the Investigator and Sponsor agree that the patient is clinically benefitting. Reasons for study discontinuation include, but are not limited to, unacceptable toxicity, disease progression, voluntary withdrawal of consent, Investigator discretion and death.	~~Patients will receive study treatment as long as it is well tolerated and both the Investigator and Sponsor agree that the patient is clinically benefitting. Reasons for study discontinuation include, but are not limited to, unacceptable toxicity, disease progression, voluntary withdrawal of consent, Investigator discretion and death.~~	Paragraph moved under Part 1 and Part 2
6.0 SYNOPSIS: Study Procedures (continued)	Dosing of PLX3397 will commence at the 600 mg/day dose level. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). On non-PK/PD paclitaxel administration days, the morning dose of PLX3397 may be administered at home, prior to paclitaxel administration. The starting dose level of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%. All patients at a given dose level	~~Dosing of PLX3397 will commence at the 600 mg/day dose level. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). On non-PK/PD paclitaxel administration days, the morning dose of PLX3397 may be administered at home, prior to paclitaxel administration. The starting dose level of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%. All patients at a given dose level~~	Paragraph moved under Part 1.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
	will be followed on treatment for at least 4 weeks before accrual to the next cohort can begin. There will be no intra-patient dose escalation permitted.	~~will be followed on treatment for at least 4 weeks before accrual to the next cohort can begin. There will be no intra-patient dose escalation permitted.~~ **Part 1 and Part 2:** **Patients will receive study treatment as long as it is well tolerated and both the Investigator and Sponsor agree that the patient is clinically benefitting. Reasons for study discontinuation include, but are not limited to, unacceptable toxicity, disease progression, voluntary withdrawal of consent, investigator discretion, and death.** **After providing informed consent, patients will undergo screening for eligibility to participate in the study. Screening will start within 28 days prior to the first study treatment dose. The physical exam and laboratory values should be obtained within 14 days prior to C1D1. Evaluations performed as part of standard-of-care and prior to informed consent may be used if they occur within the protocol-specified timeframe.**	
6.0 SYNOPSIS: Study Procedures (continued)	All female patients of child-bearing potential must have a negative urine pregnancy test within 14 days of C1D1	All female patients of child-bearing potential must have a negative urine pregnancy test within 14 days **prior to** C1D1.	Clarification that urine pregnancy test must be done prior to C1D1.
6.0 SYNOPSIS: Study Procedures (continued)	Blood samples for PLX3397 PK analysis.... Pharmacodynamic (PD) markers....	**Part 1:** Blood samples for PLX3397 PK analysis will be obtained…. **Part 1 and Part 2:** Pharmacodynamic (PD) markers....	PK samples are collected only in Part 1 while PD samples will be obtained in both Parts 1 and 2.
6.0 SYNOPSIS: Key Patient Selection	Inclusion Criteria 1. Advanced, incurable solid	Inclusion Criteria **1. Patients in:**	Once the RP2D has been determined, the efficacy and safety of PLX3397 will be

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
Criteria	tumor. *Amendment 3 does not contain Part 2.*	**Part 1: an advanced,** incurable solid tumor **Part 2: an advanced, incurable solid tumor and have received ≤2 prior chemotherapy regimens for the treatment of their primary malignancy and for whom a taxane would be considered a reasonable chemotherapy option.**	determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.
6.0 SYNOPSIS Dose Limiting Toxicities	Patients must receive at least 21 days of PLX3397 AND at least 3 doses of paclitaxel during the first 28 day cycle in order to be considered evaluable for DLT, unless doses are missed due to a DLT.	**Part 1:** Patients must receive at least 21 days of PLX3397 AND at least 3 doses of paclitaxel during the first 28 day cycle in order to be considered evaluable for DLT, unless doses are missed due to a DLT.	Criteria for Dose Limiting Toxicities refer only to Part 1.
6.0 SYNOPSIS Dosage and Regimen	At least 3 or 4 planned paclitaxel doses must be administered…. In order to initiate each weekly paclitaxel treatment, patients….	**Part 1:** At least 3 or 4 planned paclitaxel doses must be administered…. **Part 1 and Part 2:** In order to initiate each weekly paclitaxel treatment, patients….	The DLT period only applies to Part 1.
6.0 SYNOPSIS: Stopping Rules	If ≥2 of 6 patients in Dose Level -1 either experience a DLT or are unable to receive the requisite PLX3397 and paclitaxel doses in the first 28 days due to treatment-related adverse events, the combination will be considered too toxic and the study will be discontinued	**Part 1:** If ≥2 of 6 patients in Dose Level -1 either experience a DLT or are unable to receive the requisite PLX3397 and paclitaxel doses in the first 28 days due to treatment-related adverse events, the combination will be considered too toxic and the study will be discontinued.	Clarification that the stopping rules for Part 1 and Part 2 are different.
6.0 SYNOPSIS: Stopping Rules (continued)	*Amendment 3 does not contain Part 2.*	**Part 2: After ~50% of the planned approximately 15 patients (RP2D-treated patients from Part 1 and Part 2) have completed at least 2 treatment Cycles, an overall interim safety summary will be reviewed by the Medical Monitor and Principal Investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not**	Needed stopping rules for Part 2.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
		warrant continued enrolment, the study will be discontinued.	
6.0 SYNOPSIS PK Parameters		**Part 1:**	PK samples will only be collected in part 1.
6.0 SYNOPSIS PD Parameters		**Part 1 and Part 2:**	Samples for exploratory biomarkers will be collected in both Parts 1 & 2.
8.0 STUDY OBJECTIVES	This trial is designed to explore the safety of escalating doses of PLX3397 with weekly paclitaxel.	This trial is designed **as a two-part study: Part 1 (Phase 1b),** to explore the safety of escalating doses of PLX3397 with weekly paclitaxel **to establish a RP2D; and, Part 2, to determine the efficacy and safety of the PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors.**	Once the RP2D has been determined, the efficacy and safety of the PLX3397 will be determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.
9.0 DESIGN 9.1 Description	Protocol PLX108-07 is a Phase 1b open-label, sequential dose escalation trial of PLX3397 plus paclitaxel.	**Part 1:** ~~**Protocol PLX108-07**~~ **This is a nonrandomized** Phase 1b open-label, sequential dose escalation trial of PLX3397 plus paclitaxel.	Distinction made that Part 1 is the dose escalation phase of the trial.
9.0 DESIGN 9.1 Description (continued)	*Amendment 3 does not contain Part 2.*	**Part 2:** **This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 15 patients (including RP2D-treated patients from Part 1 and Part 2). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.**	Once the RP2D has been determined, the efficacy and safety of the PLX3397 will be determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.
9.0 DESIGN 9.4 Number of Patients	Enrollment is planned to include.... *Amendment 3 does not contain Part 2.*	**Part 1:** Enrollment is planned to include.... **Part 2:** **Enrollment is planned to include approximately 15 patients (including all RP2D-treated patients from Part 1 and Part 2) recruited from**	Clarified number of patients to be treated at RP2D and patient replacement rules.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
		approximately 3–4 sites. **Part 1 and Part 2:** **Patients who do not receive the requisite PLX3397 and/or paclitaxel doses in Cycle 1 due to anything other than treatment-related and/or dose-limiting toxicity may be replaced. Patients who experience an allergic reaction to paclitaxel that precludes further dosing (i.e., ≥Grade 3) will be removed from the study and may also be replaced.**	
10.1 Inclusion Criteria	Advanced, incurable solid tumor *Amendment 3 does not contain Part 2.*	**1. Patients with:** **a. Part 1: an advanced, incurable solid tumor** **b. Part 2: an advanced, incurable solid tumor and have received ≤2 prior chemotherapy regimens for the treatment of their primary malignancy and for whom a taxane would be considered a reasonable chemotherapy option.**	Once the PP2D has been determined, the efficacy and safety of the PLX3397 will be determined in patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. Efficacy and safety signals will be used to guide subsequent studies.
10.2 Exclusion Criteria	8. Known chronic Hepatitis B or C, or HIV infection	8. Known chronic **active** Hepatitis B or C, or HIV infection	Clarified that chronic active hepatitis was excluded, not a history of hepatitis B or C.
13.12 Dose-Limiting Toxicities	13.12 Dose-Limiting Toxicities	13.12 Dose-Limiting Toxicities **(Part 1 only)**	Determination of dose-limiting toxicity is limited to Part 1; Part 2 occurs after the RP2D has been determined.
13.14 PLX3397 Dose Modifications	PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 …. *Amendment 3 does not contain Part 2.* Guidelines for dosage modification for PLX3397–related toxicities as well as guidelines for their management are noted in Table 3.	**During Part 1,** PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 …. **During Part 2: PLX3397 dose reductions or interruptions for adverse events may take place at any time.** **For Part 1 and Part 2,** guidelines for dosage modification for PLX3397–related toxicities as well as guidelines for their	Added information on Part 2.

Major Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
		management are noted in Table 3.	
13.15 Paclitaxel Dose Modifications	Dose modifications or interruptions of paclitaxel are not permitted in Cycle 1 unless the patient experiences a DLT. Other dose modifications for paclitaxel will be in accordance to the product label.	Dose modifications or interruptions of paclitaxel are not permitted in **Part 1**, Cycle 1 unless the patient experiences a DLT. **For Part 1, Cycle 2 and subsequent cycles and Part 2,** other dose modifications for paclitaxel will be in accordance to the product label.	Clarified when paclitaxel dose reductions can be made.
14.0 TEST ARTICLES 14.1.1 PLX3397 Administration	On C1D1 and C1D15, the patients should take the morning dose of PLX3397 at the clinical site after the pre-dose PK blood sample is obtained– patients should be instructed not to take the study drug at home prior to these clinic visits. The time of dosing will be recorded in the clinic. The evening dose of PLX3397 should be taken by the patient at home. On all other visit days and for all visit days, patients may administer the study drug at home and record dosing information in the PLX3397 administration diary.	**For Part 1 only** on C1D1, ~~and~~ C1D15, **and the first day of all subsequent cycles,** the patients should take the morning dose of PLX3397 at the clinical site after the pre-dose PK blood sample is obtained– patients should be instructed not to take the study drug at home prior to these clinic visits. The time of dosing will be recorded in the clinic. The evening dose of PLX3397 should be taken by the patient at home. **For Part 1** on all other visit days and **for all Part 2 visit days,** patients may administer the study drug at home and record dosing information in the PLX3397 administration diary.	Clarified PLX3397 dose administration times on days of Part 1 blood samples for PK.

Minor Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
Trial Flow Chart	Plasma for PK	Plasma for PK **(Part 1 only)**	There is no PK in Part 2.
Trial Flow Chart	Pharmacodynamic (PD) markers.....	**PD biomarkers** **(Part 1 and Part 2)**	Clarified that PD biomarkers will be assessed in Part 1 and Part 2.
13.0 PROCEDURES	Multiple locations in this section: blood sample collection for PK	Multiple locations in this section: blood sample collection for PK **(Part 1 only)**	There is no PK in Part 2.
14.1.4 PLX3397 Accountability, Reconciliation, and Return		**The dates of destruction of all PLX3397 capsules must be recorded on the PLX3397 accountability log.**	Clarification for drug accountability..
18.0 PHARMACO-KINETIC EVALUATION	18.0 PHARMACOKINETIC EVALUATION	18.0 PHARMACOKINETIC EVALUATION **(Part 1 only)**	Clarified that PK is only in Part 1.
19.1 Safety Analysis	Laboratory variables will be examined using mean change in value from baseline to scheduled time points for each dose level group.	Laboratory variables will be ~~examined~~ **summarized** using mean change in value from baseline to scheduled time points for each dose level group **and 95% confidence interval**.	Clarification.
19.2 Efficacy Analysis	Response to treatment according to the RECIST criteria will be reported via descriptive statistics by dose level. The absolute and percent change from baseline for the extent of disease (sum of the longest diameters) will be summarized at each scheduled evaluation using descriptive statistics.	Response to treatment according to the RECIST criteria will be reported via descriptive statistics by dose level. The absolute and percent change from baseline for the extent of disease (sum of the longest diameters) will be summarized at each scheduled evaluation using descriptive statistics **including mean, standard deviation, minimum and maximum values.**	Clarification.
19.2 Efficacy Analysis (continued)	All patients who are eligible for efficacy analyses will be evaluable for progression-free survival, regardless of the presence or absence of measurable disease. Progression-free survival will be calculated for each patient. Progression-free survival is defined as the number of days from the	All patients who are eligible for efficacy analyses will be evaluable for progression free-survival, regardless of the presence or absence of measurable disease. Progression-free survival will be calculated for each patient **and shown for all patients on a Kaplan-Meier plot**. Progression-free survival is defined as the number of days from the first day of treatment to	Clarification.

Minor Modifications			
Section	**Amendment 3**	**Amendment 4**	**Rationale**
	first day of treatment to the date of the first documented disease progression or date of death, whichever occurs first.	the date of the first documented disease progression or date of death, whichever occurs first.	
19.2 Efficacy Analysis (continued)	In addition, relationships between antitumor activity, pharmacodynamic markers, and drug exposure levels will be explored.	~~In addition,~~ **Exploratory analyses may be conducted to evaluate possible** relationships between antitumor activity, pharmacodynamic markers, and drug exposure levels ~~will be explored~~.	Clarification.
19.4 Pharmaco-kinetic Analysis	19.4 Pharmacokinetic Analysis	19.4 Pharmacokinetic Analysis **(Part 1 only)**	Clarified that PK is only in Part 1.

ATTACHMENT 9: AMENDMENT 5 SUMMARY OF CHANGES

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes.

Major Modifications			
Section	**Amendment 4**	**Amendment 5**	**Rationale**
6.0 SYNOPSIS: Key Patient Selection Criteria	Inclusion Criteria **Part 2: an advanced, incurable solid tumor** and have received ≤2 prior chemotherapy regimens for the treatment of their primary malignancy and **for whom a taxane would be considered a reasonable chemotherapy option.**	Inclusion Criteria Part 2: an advanced, incurable solid tumor **~~and have received ≤2 prior chemotherapy regimens for the treatment of their primary malignancy and~~** for whom a taxane would be considered a reasonable chemotherapy option.	The rationale for this modification is to allow enrollment of a similar patient population in Part 2 as that for Part 1 and for whom there may be the potential for treatment benefit. There is no safety concern with this change. This modification was discussed with the principal investigators at all participating trial sites and all were in agreement with this proposed change. This modification is based on Note To File 04 February 2014.
6.0 SYNOPSIS: Study Design	Part 2: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 15 patients (including all RP2D-treated patients from Part 1 and Part 2). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.	Part 2: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately **~~15~~ 30 patients** (including all RP2D-treated patients from Part 1 and Part 2). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.	Patients who withdraw from the study due to disease progression or for any reason other than PLX3397-related adverse events need to be replaced, because at least 15 (Part 1 + Part 2) patients treated at the 1600 mg/day RP2D with 2-cycle PLX3397 exposure and safety data are required to enable PLX3397 to be studied in the I-SPY 2 trial. This modification is based on Note To File 14 April 2014.

Major Modifications			
Section	**Amendment 4**	**Amendment 5**	**Rationale**
6.0 SYNOPSIS: Number of Patients/Sites	Part 2: Enrollment is planned to include approximately 15 patients (including RP2D-treated patients from Part 1 and Part 2) recruited from 3 sites. Part 1 and Part 2: Patients who do not receive the requisite PLX3397 and/or paclitaxel doses in Cycle 1 due to anything other than treatment-related and/or dose-limiting toxicity may be replaced. Patients who experience an allergic reaction to paclitaxel that precludes further dosing (i.e., ≥Grade 3) will be removed from the study and may also be replaced.	Part 2: Enrollment is planned to include approximately ~~15~~ **30 patients** (including RP2D-treated patients from Part 1 and Part 2) recruited from 3 sites. Part 1 and Part 2: Patients who do not receive the requisite PLX3397 and/or paclitaxel doses in Cycle 1 due to anything other than treatment-related and/or dose-limiting toxicity may be replaced. Patients who experience an allergic reaction to paclitaxel that precludes further dosing (i.e., ≥Grade 3) will be removed from the study and may also be replaced.	Patients who withdraw from the study due to disease progression or for any reason other than PLX3397-related adverse events need to be replaced, because at least 15 (Part 1 + Part 2) patients treated at the 1600 mg/day RP2D with 2-cycle PLX3397 exposure and safety data are required to enable PLX3397 to be studied in the I-SPY 2 trial. This modification is based on Note To File 14 April 2014.
6.0 SYNOPSIS: Study Procedures	Part 2: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 15 patients (RP2D-treated patients from Part 1 and Part 2). Each treatment cycle will be 28 days.	Part 2: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately ~~15~~ **30 patients** (RP2D-treated patients from Part 1 and Part 2). Each treatment cycle will be 28 days.	Patients who withdraw from the study due to disease progression or for any reason other than PLX3397-related adverse events need to be replaced, because at least 15 (Part 1 + Part 2) patients treated at the 1600 mg/day RP2D with 2-cycle PLX3397 exposure and safety data are required to enable PLX3397 to be studied in the I-SPY 2 trial. This modification is based on Note To File 14 April 2014.

Major Modifications			
Section	**Amendment 4**	**Amendment 5**	**Rationale**
9.0 DESIGN 9.1 Description	Part 2: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 15 patients (including all RP2D-treated patients from Part 1 and Part 2). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.	Part 2: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately ~~15~~ **30** patients (including all RP2D-treated patients from Part 1 and Part 2). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.	Patients who withdraw from the study due to disease progression or for any reason other than PLX3397-related adverse events need to be replaced, because at least 15 (Part 1 + Part 2) patients treated at the 1600 mg/day RP2D with 2-cycle PLX3397 exposure and safety data are required to enable PLX3397 to be studied in the I-SPY 2 trial. This modification is based on Note To File 14 April 2014.
9.0 DESIGN 9.4 Number of Patients	Enrollment is planned to include approximately 15 patients (including all RP2D-treated patients from Part 1 and Part 2) recruited from 3 sites.	Enrollment is planned to include approximately ~~15~~ **30** patients (including all RP2D-treated patients from Part 1 and Part 2) recruited from 3 sites.	Patients who withdraw from the study due to disease progression or for any reason other than PLX3397-related adverse events need to be replaced, because at least 15 (Part 1 + Part 2) patients treated at the 1600 mg/day RP2D with 2-cycle PLX3397 exposure and safety data are required to enable PLX3397 to be studied in the I-SPY 2 trial. This modification is based on Note To File 14 April 2014.
10.1 Inclusion Criteria	Inclusion Criteria **Part 2: an advanced, incurable solid tumor** and have received ≤2 prior chemotherapy regimens for the treatment of their primary malignancy and **for whom a taxane would be considered a reasonable chemotherapy option.**	Inclusion Criteria **Part 2: an advanced, incurable solid tumor** ~~and have received ≤2 prior chemotherapy regimens for the treatment of their primary malignancy and~~ **for whom a taxane would be considered a reasonable chemotherapy option.**	The rationale for this modification is to allow enrollment of a similar patient population in Part 2 as that for Part 1 and for whom there may be the potential for treatment benefit. There is no safety concern with this change. This modification was discussed with the principal investigators at all participating trial sites and all were in agreement with this proposed change. This modification is based on Note To File 04 February 2014.

Major Modifications			
Section	**Amendment 4**	**Amendment 5**	**Rationale**
16.5 Safety Laboratory Determinations		Patients enrolling in studies with PLX3397 who are also receiving concomitant warfarin should have their anti-coagulation status carefully monitored, especially shortly after initiation of PLX3397, for the potential need to make adjustments in warfarin dosing. In particular, INR should be obtained just prior to initiation of PLX3397, within 1-2 weeks after initiation, and periodically thereafter. Dose adjustments of warfarin should be made as medically indicated.	Review of pharmacokinetic data and INR data in a small number of patients taking PLX3397 and warfarin is inconclusive as to whether there is a drug-drug interaction; however, a potential drug-drug interaction between PLX3397 and warfarin could exist. This modification is based on Note To File 07 October 2013.

ATTACHMENT 10: AMENDMENT 6 SUMMARY OF CHANGES

Note: Changes throughout the protocol that are repetitive, self-evident or grammatical may not be individually listed in this Summary of Changes.

Section	Amendment 5	Amendment 6	Rationale
4.3 SAE Reporting Contact	**Name:** [redacted] **Address:** Alba BioPharm Advisors, Inc. 12109 Betts Lane Raleigh, NC 27614 **Phone:** [redacted] **Cell:** [redacted] **Fax:** [redacted] **Email:** [redacted]	**Name:** **SynteractHCR Safety SAE Facsimile** **Phone:** [redacted] **Fax:** [redacted] **Email:** [redacted]	To update safety contact
5.0 List of Abbreviations	*Amendment 5 does not contain these abbreviations in this section.*	**EDC** — **Electronic Data Capture** **FACS** — **Flow cytometry** **Fms** — **Colony stimulating factor 1 receptor** **MDSC** — **Myeloid-derived suppressor cell**	To add new abbreviations used in the protocol amendment
6.0 SYNOPSIS Study Objectives	**Part 1** (Phase 1b), to explore the safety of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D; and, **Part 2**, to determine the efficacy and safety of the PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors. The primary objective of this Phase 1b study is to establish the dose limiting toxicities (DLTs) **and** recommended Phase **2** dose (RP2D) of PLX3397 when given in combination with weekly standard dose paclitaxel in patients with advanced solid tumors. The secondary objectives of	**Part 1 ~~(Phase 1b)~~: The primary objective is to explore the safety and tolerability** of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D~~;~~ ~~and,~~ **The secondary objectives are to explore the efficacy and pharmacokinetics (PK) of PLX3397 in combination with paclitaxel in patients with advanced solid tumors.** **Part 2: The primary objective is ~~to determine the efficacy and safety~~ to confirm the safety and tolerability** of ~~the~~ PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors**. The secondary objective is to explore the efficacy of PLX3397 in combination with paclitaxel in**	To add Part 3 to explore the efficacy and safety of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

Section	Amendment 5	Amendment 6	Rationale
	this study are to 1) evaluate the overall safety and tolerability of PLX3397 in combination with paclitaxel, 2) explore the efficacy of PLX3397 in combination with paclitaxel in patients with advanced solid tumors, and 3) determine the pharmacokinetics (PK) of PLX3397 when administered in combination with paclitaxel. Exploratory objectives include correlating the change in Colony Stimulating Factor-1 (CSF-1) levels during treatment with specific dose levels of PLX3397 and identifying new biomarkers of clinical activity.	**patients with advanced solid tumors.** ~~The primary objective of this Phase 1b study is to establish the dose limiting toxicities (DLTs) recommended Phase 2 dose (RP2D) of PLX3397 when given in combination with weekly standard dose paclitaxel in patients with advanced solid tumors.The secondary objectives of this study are to 1) evaluate the overall safety and tolerability of PLX3397 in combination with paclitaxel, 2) explore the efficacy of PLX3397 in combination with paclitaxel in patients with advanced solid tumors, and 3) determine the pharmacokinetics (PK) of PLX3397 when administered in combination with paclitaxel.~~ **Part 1 and 2:** Exploratory objectives include correlating the change in Colony Stimulating Factor-1 (CSF-1) levels during treatment with specific dose levels of PLX3397 and identifying new biomarkers of clinical activity. **Part 3: The primary objective is to determine the efficacy of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. The secondary objectives are to explore the effect of PLX3397 on cancer tissue and blood biomarkers and the safety and tolerability of PLX3397 in combination with paclitaxel in this patient population.**	

Section	Amendment 5	Amendment 6	Rationale
6.0 SYNOPSIS Study Design	**Part 1**: This is a nonrandomized, open-label phase 1b study employing a standard 3+3 dose escalation design to determine the RP2D of PLX3397, a novel inhibitor of the CSF-1 receptor (Fms), when administered in combination with paclitaxel in patients with advanced solid tumors. **Part 2**: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (including all RP2D-treated patients from Part 1 and Part 2). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.	**Part 1**: This is a nonrandomized, open-label ~~phase 1b~~ study employing a standard 3+3 dose escalation design to determine the RP2D of PLX3397, a novel inhibitor of the CSF-1 receptor (Fms), when administered in combination with paclitaxel in patients with advanced solid tumors. **Part 2**: This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (including all RP2D-treated patients from Part 1 and Part 2). The ~~patient~~ **candidate** population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. **This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients. The candidate population will be patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Patients must be resistant or refractory to prior platinum-based standard care systemic regimens or refractory to primary treatment with a platinum-containing regimen. Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms: 1) daily PLX3397 at the RP2D; 2) weekly paclitaxel; and 3) daily PLX3397 at the RP2D and weekly paclitaxel. Cancer tissue (biopsy) and blood for biomarkers will be obtained during Screening and at Cycle 1**	To add Part 3 to explore the efficacy and safety of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

Section	Amendment 5	Amendment 6	Rationale
		Day 28 ± 7 days (Cycle 1 Day 21 to Cycle 1 Day 35). **Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with daily PLX3397 at the RP2D and weekly paclitaxel. Cycle 2 and all subsequent cycles will be 28-day cycles. Blood biomarkers will be obtained prior to treatment on Day 1 of all subsequent cycles and the End-of-Study Visit. Patients will have efficacy assessments every 8 weeks to determine objective response (CR + PR), clinical benefit (CR + PR + SD), progression-free survival (PFS), and time to next treatment.**	
6.0 SYNOPSIS Number of Patients/Sites	*Amendment 5 does not contain Part 3.*	**Part 3:** **Enrollment is planned to include up to approximately 30 patients recruited from approximately 3–6 sites to accrue 18 patients who can provide pretreatment and end-of-Cycle 1 cancer tissue and are evaluable for determining response using RECIST 1.1 criteria. Patients unable to provide the sequential cancer tissue samples or non-evaluable for response using RECIST criteria will be replaced.**	To add Part 3 to explore the efficacy and safety of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
6.0 SYNOPSIS Study Treatments	**Part 1:** PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. The starting dose of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%. **Part 2:** PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. The dose of PLX3397 will be	**Part 1:** PLX3397 will be administered orally, twice daily (BID) using a continuous dosing regimen. The starting dose of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%. ~~**Part 1 and Part 2:**~~ Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. **One paclitaxel dose may be omitted per cycle by physician discretion after Cycle 1.**	To add Part 3 to explore the efficacy and safety of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

Section	Amendment 5	Amendment 6	Rationale
	the RP2D. There will be no dose escalation. **Part 1 and Part 2:** Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. One paclitaxel dose may be omitted per cycle by physician discretion after Cycle 1. Study treatment will be provided until disease progression, unacceptable or dose-limiting toxicity, death, withdrawal of consent, study termination by Sponsor, or if the Investigator and patient agree that it is in the patient's best interests to discontinue.	**Part 2:** PLX3397 will be administered orally, twice daily (BID using a continuous dosing regimen. The dose of PLX3397 will be the RP2D. There will be no dose escalation. **Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle.** One paclitaxel dose may be omitted per cycle by physician discretion after Cycle 1. **Part 3: Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms:** **4) PLX3397 600 mg BID using a continuous dosing regimen** **5) Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes** **6) PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes** **Following the second cancer tissue and blood for biomarker sampling during the period from Study Day 28 - 35, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with**	

Section	Amendment 5	Amendment 6	Rationale
		PLX3397. **Part 1, Part 2, and Part 3:** Study treatment will be provided until disease progression, unacceptable or dose-limiting toxicity, death, withdrawal of consent, study termination by Sponsor, or if the Investigator and patient agree that it is in the patient's best interests to discontinue.	
6.0 SYNOPSIS Study Procedures	**Part 1:** This nonrandomized, open-label study will employ a traditional 3+3 Phase 1 design, with escalating dosing cohorts of PLX3397 and a fixed dose level of paclitaxel. Each treatment cycle will be 28 days. Dosing of PLX3397 will commence at the 600 mg/day dose level. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). On non-PK/PD paclitaxel administration days, the morning dose of PLX3397 may be administered at home, prior to paclitaxel administration. The starting dose level of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%. All patients at a given dose level will be followed on treatment for at least 4 weeks before accrual to the next cohort can begin. There will be no intra-patient dose escalation permitted. PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 **only if a patient experiences a DLT.** PLX3397 interruptions during Cycle 1 are also	**Part 1:** This nonrandomized, open-label study will employ a traditional 3+3 Phase 1 design, with escalating dosing cohorts of PLX3397 and a fixed dose level of paclitaxel. Each treatment cycle will be 28 days. Dosing of PLX3397 will commence at the 600 mg/day dose level. Patients should fast (1 hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). On non-PK/PD paclitaxel administration days, the morning dose of PLX3397 may be administered at home, prior to paclitaxel administration. ~~The starting dose level of PLX3397 will be 600 mg/day.~~Dose escalation will occur in increments of ≤50%. All patients at a given dose level will be followed on treatment for at least 4 weeks before accrual to the next cohort can begin. There will be no intra-patient dose escalation permitted. PLX3397 dose reductions and interruptions will be permitted during the first 28 days of Cycle 1 **only if a patient experiences a DLT.** PLX3397 interruptions during Cycle 1 are also permitted for Grade 3 vomiting that persists despite optimal supportive care. If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be permitted at the	To add Part 3 to explore the efficacy and safety of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

Section	Amendment 5	Amendment 6	Rationale
	permitted for Grade 3 vomiting that persists despite optimal supportive care. If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be permitted at the discretion of the Investigator and in consultation with the Medical Monitor. After C1D28, dose reductions or interruptions for adverse events may take place at any time. **Part 2:** This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (RP2D-treated patients from **Part 1** and **Part 2**). Each treatment cycle will be 28 days. Dosing of PLX3397 will commence at the RP2D. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). There will be no intra-patient dose escalation permitted. PLX3397 dose reductions or interruptions for adverse events may take place at any time. **Part** 1 and **Part 2:** Patients will receive study treatment as long as it is well tolerated and both the … Patients will be monitored throughout the study for adverse events and compliance with study drug administration. **Part 1:** Blood samples for PLX3397 PK analysis will be obtained pre-PLX3397 and paclitaxel dosing on C1D1, pre-	discretion of the Investigator and in consultation with the Medical Monitor. After C1D28, dose reductions or interruptions for adverse events **(AEs)** may take place at any time. **Part 2:** This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (RP2D-treated patients from **Part 1** and **Part 2**). Each treatment cycle will be 28 days. Dosing of PLX3397 will commence at the RP2D. Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). There will be no intra-patient dose escalation permitted. PLX3397 dose reductions or interruptions for ~~adverse events~~ **AEs** may take place at any time. **Part 3:** **The candidate population will be patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer.** **Patients will be sequentially assigned to one of three Cycle 1 (28-day) lead-in treatment arms:** **4) PLX3397 600 mg BID using a continuous dosing regimen** **5) Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes** **6) PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately**	

Section	Amendment 5	Amendment 6	Rationale
	PLX3397 and paclitaxel dosing on C1D15, and 2 and 4 hours post-PLX3397 and paclitaxel dosing on C1D15. **Part 1 and Part 2:** Pharmacodynamic (PD) markers including serum CSF-1 will be obtained at pre-dose on Day 1 of each cycle as outlined in the Trial Flow Chart. A whole blood sample for circulating CD14/CD16 positive monocyte analysis will also be obtained pre-dose on C1D1 and C1D1.	**60 minutes** **Following the second cancer biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with PLX3397.** **Patients should fast (one hour) before and after PLX3397 administration (see guidelines in Section 14.1.1). There will be no intra-patient dose escalation permitted. PLX3397 dose reductions or interruptions for AEs may take place at any time.** **Part 1, Part 2, and Part 3:** Patients will receive study treatment as long as it is well tolerated and both the … Patients will be monitored throughout the study for ~~adverse events~~**AEs** and compliance with study drug administration. **Part 1:** Blood samples for PLX3397 PK analysis will be obtained pre-PLX3397 and paclitaxel dosing on C1D1, pre-PLX3397 and paclitaxel dosing on C1D15, and 2 and 4 hours post-PLX3397 and paclitaxel dosing on C1D15. **Part 1, Part 2, and Part 3:** Pharmacodynamic (PD) markers including serum CSF-1 will be obtained at pre-dose on Day 1 of each cycle as outlined in the Trial Flow Chart. A whole blood sample for circulating	

Section	Amendment 5	Amendment 6	Rationale
		CD14/CD16 positive monocyte analysis will also be obtained pre-dose on C1D1 and C1D15. **Part 3:** **Cancer tissue [2-3 core biopsies of target (≥2 cm diameter) or non-target lesions] and blood for biomarkers will be obtained during Screening after CT imaging and at Cycle 1 Day 28 ± 7 days (Cycle 1 Day 21 to Cycle 1 Day 35).. Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with daily PLX3397 at the RP2D and weekly paclitaxel. Cycle 2 and all subsequent cycles will be 28-day cycles. A blood sample for plasma PK and biomarkers will be obtained pre-PLX3397 and paclitazel dosing on Cycle 1Day 1, Cycle 1Day 15 and on Day 1 of all subsequent cycles and the End-of-Study Visit. Patients will have efficacy assessments every 8 weeks to determine objective response (CR + PR), clinical benefit (CR + PR + SD), progression-free survival (PFS), and time to next treatment (after last study treatment). CA-125 sampling requirements: 2 pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of starting therapy; subsequent samples on the first day of each cycle starting with C2D1 and End-of-Study Visit.**	

Section	Amendment 5	Amendment 6	Rationale
6.0 SYNOPSIS Key Patient Selection Criteria Inclusion Criteria AND 10.1 Inclusion Criteria	Inclusion Criteria 1. Patients in a. Part 1: an advanced, incurable solid tumor b. Part 2: an advanced, incurable solid tumor for whom a taxane would be considered a reasonable chemotherapy option. 2. Patients with stable brain metastases are eligible for this trial. However, patients must not have required steroid treatment for their brain metastases within 30 days of Screening. 3. Bone-directed therapy (e.g., bisphosphonates or denosumab) is permitted. However, patients should not have started bone-directed therapy within 2 weeks of C1D1, and new bone-directed therapy should not be initiated during the first 4 weeks of study (i.e., Cycle 1). 4. Washout from any prior investigational therapy of at least 28 days prior to C1D1. 17. Ability to give written informed consent and willing to comply with the requirements of the protocol	Inclusion Criteria **1.** Patients in a. Part 1: an advanced, incurable solid tumor b. Part 2: an advanced, incurable solid tumor for whom a taxane would be considered a reasonable chemotherapy option. **c. Part 3: advanced, metastatic or non-resectable epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with:** **i. platinum-resistant cancer, defined as disease that responded to a platinum-containing chemotherapy regimen, but demonstrated recurrence within six months following the completion of that platinum-containing regimen,** **OR** **ii. platinum-refractory cancer, defined as disease failed to achieve at least a partial response to a platinum-containing regimen (i.e., stable disease or actual disease progression),** **AND** **iii. have not been treated with a taxane within one year of C1D1,** **AND** **iv. have not been treated with weekly paclitaxel after first-line treatment in which weekly paclitaxel plus a platinum is permitted.** 2. **Part 3: Patients must have**	To add Part 3 inclusion criteria

Section	Amendment 5	Amendment 6	Rationale
		target (≥2 cm diameter) or non-target lesion cancer that is accessible for 2-3 core biopsies during Screening after CT imaging and all other screening tests and procedures have been completed and during the period from Cycle 1 Day 21 to Cycle 1 Day 35. ~~2~~ 3. Patients with stable brain metastases are eligible for this trial. However, patients must not have required steroid treatment for their brain metastases within 30 days of Screening. ~~3~~ 4. Bone-directed therapy (e.g., bisphosphonates or denosumab) is permitted. However, patients should not have started bone-directed therapy within 2 weeks of C1D1, and new bone-directed therapy should not be initiated during the first 4 weeks of study (i.e., Cycle 1).\ ~~4~~ 5. Washout from any prior investigational therapy of at least ~~28 days~~ **five times the** $T_{1/2}$ prior to C1D1. ~~5~~ **6. Washout from any prior biologic or targeted therapy at least 4 weeks or five times the T1/2 (whichever is shorter) prior to C1D1.** ~~17~~19. Ability to give written informed consent and willing to comply with the requirements of the protocol; **and for Part 3, able to give written informed consent for 2 cancer biopsy procedures.**	

Section	Amendment 5	Amendment 6	Rationale
6.0 SYNOPSIS Dose Limiting Toxicities	Non-hematologic DLTs • Any CTCAEv4 Grade ≥3 non-hematologic toxicity, **unless the event is clearly unrelated** to treatment with PLX3397 in combination with weekly standard fixed dosing of paclitaxel EXCEPT the following:	~~Non-hematologic~~ **Other** DLTs • Any CTCAEv4 Grade ≥3 ~~non-hematologic~~ **other** DLTs toxicity, **unless the event is clearly unrelated** to treatment with PLX3397 in combination with weekly standard fixed dosing of paclitaxel EXCEPT the following:	
6.0 SYNOPSIS Dosage and Regimen	PLX3397 (100 or 200 mg capsules) will be administered orally, using a dosing regimen of twice daily on an empty stomach (see Section 14.1.1 for details). The BID regimen is preferred to reduce capsule load per dose and minimize intra-day drug level fluctuations. On non-PK paclitaxel dosing days, PLX3397 may be administered at home, prior to the clinic visit for paclitaxel administration. Paclitaxel at a fixed dose of 80 mg/m2 will be administered IV over approximately 60 minutes once weekly (±48 hours). **Part 1:** At least 3 of 4 planned paclitaxel doses must be administered in the DLT period (i.e., Cycle 1). On subsequent cycles, 1 paclitaxel dose may be skipped per Cycle per Investigator discretion and/or patient preference. **Part 1 and Part 2:** In order to initiate each weekly paclitaxel treatment, patients must have an ANC ≥1000/mm^3 and platelets ≥75,000/mm^3. A paclitaxel premedication regimen, consisting of a corticosteroid, an H2	PLX3397 (~~100 or~~ 200 mg capsules) will be administered orally, using a dosing regimen of twice daily**. Patients should fast (one hour) before and after PLX3397 administration** on an empty stomach (see Section 14.1.1 for details). The BID regimen is preferred to reduce capsule load per dose and minimize intra-day drug level fluctuations. On non-PK ~~paclitaxel~~ **or non-blood biomarker** dosing days, PLX3397 may be administered at home, prior to the clinic visit for paclitaxel administration. ~~Paclitaxel at a fixed dose of 80 mg/m2 will be administered IV over approximately 60 minutes once weekly (±48 hours).~~ **Part 1:** At least 3 of 4 planned paclitaxel doses must be administered in the DLT period (i.e., Cycle 1). On subsequent cycles, 1 paclitaxel dose may be skipped per Cycle per Investigator discretion and/or patient preference. ~~**Part 1 and**~~ **Part 2:** **Patients will be treated with PLX3397 RP2D (600 mg BID) using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. One paclitaxel dose may be omitted per cycle by physician discretion.**	To add Part 3 to dosage and regimen

Section	Amendment 5	Amendment 6	Rationale
	antagonist and diphenhydramine, is recommended in order to reduce the risk of anaphylaxis.	**Part 3: Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms:** • **PLX3397 600 mg BID using a continuous dosing regimen.** • **Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes.** • **PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes.** **Following the second cancer tissue and blood for biomarker sampling during the period from Study Day 28 - 35, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with PLX3397.** **Part 1, Part 2, and Part 3:** In order to initiate each weekly paclitaxel treatment, patients must have an ANC ≥1000/mm^3 and platelets ≥75,000/mm^3. A paclitaxel premedication regimen, consisting of a corticosteroid, an H2 antagonist and diphenhydramine, is recommended in order to reduce the risk of anaphylaxis.	
6.0 SYNOPSIS Safety and	*Amendment 5 does not contain Part 3.*	**Part 3: AE and serious adverse event (SAE) reporting will**	To add start of AE collection for Part 3 of the

Section	Amendment 5	Amendment 6	Rationale
Tolerability Assessments		**commence when the 2-3 core biopsies are obtained during Screening.**	study
6.0 SYNOPSIS Stopping Rules	*Amendment 5 does not contain Part 3.*	**Part 3:** **After ~50% of the planned approximately 18 patients have completed at least 2 treatment Cycles, an overall interim safety summary will be reviewed by the Medical Monitor and Principal Investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not warrant continued enrolment, the study will be discontinued**.	To add stopping rules for Part 3 of the study
6.0 SYNOPSIS PK Parameters	**Part 1:**	**Part 1 and Part 3:**	To add PK parameters for Part 3 of the study
6.0 SYNOPSIS PD Parameters	**Part 1 and Part 2:** Exploratory biomarkers for evaluating anti-tumor activity, inflammation and energy metabolism may be measured. Biomarkers will include, but are not limited to, CSF-1.	**Part 1, Part 2, and Part 3:** Exploratory biomarkers for evaluating anti-tumor activity, inflammation and energy metabolism may be measured. Biomarkers will include, but are not limited to, CSF-1. **Part 3:** **Cancer tissue biomarkers will include:** • **IHC for CD68, CD8, PD-L1, and additional markers of macrophage and T-cell presence and function** • **RNA expression analysis for an exploratory panel of tumor microenvironment markers** • **Staining of cells of the tumor microenvironment. Panels of IHC markers specific for macrophages, T-cells, and other immune and inflammatory cells will be employed, for semi-quantitative changes in cell number, location within the tumor, and degree of activation.**	To add PD parameters for Part 3 of the study

Section	Amendment 5	Amendment 6	Rationale
		Blood biomarkers will include: • **CA-125 sampling requirements: two pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of C1D1; subsequent samples on the first day of each cycle starting with C2D1 and End-of-Study Visit.** • **Plasma CSF-1 and additional markers of treatment effect** • **Whole blood CD14/CD16 monocyte subset by FACS analysis** • **Whole blood myeloid-derived suppressor cell (MDSC) by FACS analysis**	
6.0 SYNOPSIS Trial Flow Chart (Part 1 and 2)		**16. End of Study imaging should be obtained for patients who go off study for reasons other than radiographic disease progression.**	To clarify which subjects should receive radiographic assessments should be obtained for End of Study imaging.
6.0 SYNOPSIS Trial Flow Chart	*Amendment 5 does not contain a Trial Flow Chart for Part 3.*	**Trial Flow Chart (Part 3)**	To add Trial Flow Chart or Part 3 of the study
7.0 INTRODUCTION		**CSF-1 Receptor Inhibition in Ovarian Cancer** **In human epithelial ovarian cancer, CSF-1 and/or Fms expression has been observed in the large majority of cases, with 75% of primary tumors and 69% of the metastases expressing CSF-1, and 92% of primary tumors and 83% of metastases expressing Fms (Kacinski 1991, Chambers 1997, Toy 2001). At the time of diagnosis in epithelial ovarian cancer patients, elevated levels of both serum and ascitic fluid CSF-1 are associated with a poor outcome (Price 1993, Scholl 1994). During the course of the disease, elevated levels of**	To add rationale for the additional indication of ovarian cancer.

Section	Amendment 5	Amendment 6	Rationale
		serum CSF-1 can herald disease recurrence or progression (Kacinski 1989). Elevated CSF-1 levels as part of a panel of markers, including CA125, has recently been shown to help improve early detection of ovarian cancer (Skates 2004, Zhang 2007). This strong association with disease detection and prognosis suggests an etiological role for Fms/CSF-1 in ovarian cancer initiation and neoplastic progression. **Based on the findings discussed above, it seems reasonable to postulate that blockade of cellular and/or molecular programs enhancing macrophage recruitment in epithelial ovarian cancer may result in decreased macrophage presence in epithelial ovarian tumors.** **PLX3397 as a macrophage-targeted tumor sensitizer** **PLX3397 is a novel, orally active, small molecule inhibitor intended for oral administration that targets 3 kinases: 1) Fms (also referred to as CSF-1R, the receptor for CSF-1 [also known as macrophage-colony stimulating factor] as well as the ligand interleukin-34 [IL-34]); 2) Kit, the receptor for stem cell factor (SCF); and 3) oncogenic Flt3, the receptor for Flt3 ligand. However, it otherwise remains highly selective in terms of impact on the activity of other receptors and kinases. The potent inhibition of these 3 kinases can be exploited to attack tumors through a variety of mechanisms: 1) direct inhibition of oncogenic drivers such as oncogenic Kit and Flt3 mutant proteins; 2) inhibition of paracrine loops between stromal cells and tumors; 3) blockade of**	

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		migration and angiogenesis; 4) blockage of CSF-1-dependent myeloid-derived suppressor cells; and 5) disruption of osteolytic metastases. **An important role for tumor-infiltrating macrophages in tumor progression has pointed to Fms as a key target in multiple tumor types (Ruffell 2015). The pro-tumorigenic role of CSF1 and Fms is supported by a wealth of studies demonstrating that CSF-1 levels predict a poor outcome in a variety of oncology indications, including breast, ovarian, non-small cell lung, and colorectal cancers.**	
8.0 STUDY OBJECTIVES	This trial is designed as a two-part study: **Part 1** (Phase 1b), to explore the safety of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D; and, **Part 2**, to determine the efficacy and safety of the PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors. **Primary Objective:** • Establish the dose limiting toxicities (DLTs) and recommended Phase 2 dose (RP2D) of PLX3397 when given in combination with weekly standard dose paclitaxel in patients with advanced solid tumors. • **Secondary Objectives:**Evaluate the overall safety and tolerability of	This trial is designed as a ~~two~~ **3-**part study: **Part 1** (Phase 1b), to explore the safety of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D; ~~and,~~ **Part 2**, to determine the efficacy and safety of the PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors**; and Part 3, to determine the efficacy and safety of PLX3397600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.** **<u>Part 1 (Phase 1b)</u>** **Primary Objective:** • To explore the safety and tolerability of escalating doses of PLX3397 with weekly paclitaxel to establish a RP2D ~~Establish the dose limiting toxicities (DLTs) and recommended Phase~~	To add Part 3 to explore the efficacy and safety of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

Section	Amendment 5	Amendment 6	Rationale
	PLX3397 in combination with paclitaxel 1. Explore the efficacy of PLX3397 in combination with paclitaxel in patients with advanced solid tumors 2. Determine the pharmacokinetics (PK) of PLX3397 when administered in combination with paclitaxel. **Exploratory Objectives:** • Correlate the change in Colony Stimulating Factor - 1 (CSF-1) levels during treatment with specific dose levels of PLX3397 • Identifying new biomarkers of clinical activity.	~~2 dose (RP2D) of PLX3397 when given in combination with weekly standard dose paclitaxel in patients with advanced solid tumors.~~ **Secondary Objectives:** • **To explore the efficacy and pharmacokinetics (PK) of PLX3397 in combination with paclitaxel in patients with advanced solid tumors.** **Part 2** **Primary Objective:** • **To confirm the safety and tolerability of PLX3397 administered at the RP2D in combination with paclitaxel in patients with advanced, non-resectable solid tumors** **Secondary Objective:** • **To explore the efficacy of** ~~Evaluate the overall safety and tolerability of~~ PLX3397 in combination with paclitaxel **in patients with advanced solid tumors** • ~~Explore the efficacy of PLX3397 in combination with paclitaxel in patients with advanced solid tumors~~ • ~~Determine the pharmacokinetics (PK) of PLX3397 when administered in combination with paclitaxel.~~ **Parts 1 and 2** **Exploratory Objectives:** • **To** correlate the change in ~~Colony Stimulating Factor - 1 (~~CSF-1~~)~~ levels during treatment with	

Section	Amendment 5	Amendment 6	Rationale
		specific dose levels of PLX3397 • **To** identify ~~ing~~ new biomarkers of clinical activity **Part 3** **Primary Objective:** • To determine the efficacy of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer **Secondary Objectives:** • To evaluate the safety and tolerability of PLX3397 in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer • To explore the effect of PLX3397 on cancer tissue and blood biomarkers	

Section	Amendment 5	Amendment 6	Rationale
9.1 Description	... **Part 2:** This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (including all RP2D-treated patients from **Part 1** and **Part 2**). The patient population will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate.	**… Part 2:** This is a nonrandomized, open-label study of PLX3397 administered at the RP2D in combination with paclitaxel in approximately 30 patients (including all RP2D-treated patients from **Part 1** and **Part 2**). The ~~patient population~~ **candidate population** will be patients with advanced solid tumors in which treatment with a taxane is considered by the investigator to be appropriate. **Part 3:** **This is a nonrandomized, open-label study of PLX3397 600 mg BID administered in combination with paclitaxel in approximately 30 patients. The candidate population will be patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Patients must be resistant or refractory to prior platinum-based standard care systemic regimens or refractory to primary treatment with a platinum-containing regimen. Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms: 1) daily PLX3397 600 mg BID; 2) weekly paclitaxel; and 3) daily PLX3397 600 mg BID and weekly paclitaxel. Cancer tissue and blood for biomarkers will be obtained during Screening and during the period from Cycle 1 Day 21 to Cycle 1 Day 35. Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with daily PLX3397 600 mg BID and weekly paclitaxel. Cycle 2 and all subsequent cycles will be 28-day**	To add Part 3 to explore the efficacy and safety of PLX3397 600 mg BID administered in combination with paclitaxel in patients with advanced, metastatic or non-resectable, platinum-resistant or -refractory epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer

Section	Amendment 5	Amendment 6	Rationale
		cycles.	
9.2 Route and Regimen	PLX3397 will be administered orally, twice daily (i.e., BID) in capsule form at the dose levels described in Section 9.1. The BID regimen is recommended at higher dose levels (e.g., ≥600 mg/day) to reduce the capsule load and minimize intra-day drug level fluctuations. A fixed dose level of paclitaxel, 80 mg/m^2, will be administered intravenously, once weekly (±48 hours). Patients must receive at least 3 of 4 paclitaxel doses during the DLT period (i.e., Cycle 1) in order to be considered evaluable for DLT, unless doses are missed due to a DLT. One dose of paclitaxel may be skipped per Cycle for subsequent cycles (i.e., Cycle 2+) per Investigator discretion and/or patient preference. In general, two consecutive doses of paclitaxel should not be skipped.	**Part 1:** PLX3397 will be administered orally, twice daily (~~i.e.,~~ BID) in capsule form **using a continuous dosing regimen** ~~at the dose levels described in Section 9.1~~. The BID regimen is recommended at higher dose levels (e.g., ≥600 mg/day) to reduce the capsule load and minimize intra-day drug level fluctuations. **The starting dose of PLX3397 will be 600 mg/day. Dose escalation will occur in increments of ≤50%.** A fixed dose level of paclitaxel 80 mg/m^2 will be administered intravenously, once weekly (±48 hours). Patients must receive at least 3 of 4 paclitaxel doses during the DLT period (i.e., Cycle 1) in order to be considered evaluable for DLT, unless doses are missed due to a DLT. One dose of paclitaxel may be skipped per Cycle for subsequent cycles (i.e., Cycle 2+) per Investigator discretion and/or patient preference. In general, two consecutive doses of paclitaxel should not be skipped. **Part 2:** **PLX3397 will be administered orally, BID using a continuous dosing regimen. The dose of PLX3397 will be the RP2D. There will be no dose escalation. Paclitaxel, 80 mg/m^2 IV will be administered weekly (±48 hours) over approximately 60 minutes in each 28-day treatment cycle. One paclitaxel dose may be omitted per cycle by physician discretion after Cycle 1.** **Part 3:** **Patients will be sequentially assigned to one of three Cycle 1 (28 to 35 day) lead-in treatment arms:** **1) PLX3397 600 mg BID using**	To add Part 3 to route and regimen

Section	Amendment 5	Amendment 6	Rationale
		a continuous dosing regimen **2) Paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes** **3) PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel, 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes** **Following the second biopsy, Cycle 1 ends and all patients will start Cycle 2 treatment with PLX3397 600 mg BID using a continuous dosing regimen and paclitaxel 80 mg/m^2 IV weekly (±48 hours) over approximately 60 minutes. Cycle 2 and all subsequent cycles will be 28-day cycles. Starting with Cycle 2, one paclitaxel dose may be omitted per cycle by physician discretion. Patients who discontinue paclitaxel due to paclitaxel-related toxicity may continue treatment with PLX3397.** **Part 1, Part 2, and Part 3:** **Study treatment will be provided until disease progression, unacceptable or dose-limiting toxicity, death, withdrawal of consent, study termination by Sponsor, or if the Investigator and patient agree that it is in the patient's best interests to discontinue.**	
9.4 Number of Patients	*Amendment 5 does not contain Part 3.*	**Part 3:** **Enrollment is planned to include up to approximately 30 patients to accrue 18 patients who can provide pretreatment and end-of-Cycle 1 cancer tissue and are evaluable for determining response using RECIST 1.1 criteria. Patients unable to provide the sequential cancer tissue samples or non-evaluable for response using RECIST**	To add Part 3 to number of subjects

Section	Amendment 5	Amendment 6	Rationale
		criteria will be replaced.	
10.3 Screen Failures	Patients who sign an informed consent form, are not assigned to a treatment, and do not receive test article are defined as screen failures. For all screen failures, the investigator will enter the screening number, patient initials and reason(s) for screen failure into the electronic data capture system (EDC). These data will also be retained in the investigator's study files and can be printed by the site in log format at the end of the study.	Patients who sign an informed consent form, are not assigned to a treatment, and do not receive test article are defined as screen failures. For all screen failures, the investigator will enter the screening number, patient initials and reason(s) for screen failure into ~~the electronic data capture system (EDC)~~ **a screen failure log**. This data will also be retained in the investigator's study files and can be printed by the site in log format at the end of the study. **In Part 3, patient data will be collected in the electronic data capture (EDC) system from the date the biopsy is performed during screening. Data will not be collected in the EDC for patients who are screen failures and have not had a biopsy assessment.**	To update screen failure procedures for Part 3
13.1 Screening	*Amendment 5 does not contain Part 3 for this section.*	**10. Part 3 only: Cancer tissue [2-3 core biopsies of target (≥2 cm diameter) or non-target lesions] for biomarkers after CT imaging and all other screening tests and procedures have been completed** **11. Part 3 only: CA-125 sampling within 3 months of starting therapy** **14. Part 3 only: Serious adverse event reporting will commence when the 2-3 core biopsies are obtained during Screening.** **The following Screening assessments must be performed within 7 days before study drug administration on Cycle 1 Day 1:** • **Part 3 only: CA-125 sampling**	To update study procedures to include Part 3 procedures

Section	Amendment 5	Amendment 6	Rationale
13.2 Pre-treatment (Baseline)	6. Pre-PLX3397 dose blood sample collection for PK **(Part 1 only)** and PD analyses. 7. Pre-PLX3397 dose whole blood sample collection for CD14/CD16 monocyte analysis. Per instructions in the Laboratory Manual, this sample is time sensitive and must be shipped out the same day as the collection, refrigerated but not frozen. 8. PLX3397 administration. Patients should fast for at least 1 hr prior to and after PLX3397 administration (see Section 14.1.1). 9. Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies). 10. Paclitaxel administration.	6. Pre-PLX3397 dose blood sample collection for plasma PK **(Part 1 and Part 3 only)** and PD **biomarker** analyses. 7. Pre-PLX3397 dose whole blood sample collection for CD14/CD16 monocyte analysis. Per instructions in the Laboratory Manual, this sample is time sensitive and must be shipped out the same day as the collection, refrigerated but not frozen. **8. Part 3 only: Pre-PLX3397 dose whole blood sample collection for myeloid-derived suppressor cell (MDSC)** 9. **Part 1, Part 2, and Part 3 (PLX3397 only and PLX3397 + paclitaxel arms):** PLX3397 administration. Patients should fast for at least 1 hour prior to and after PLX3397 administration (see Section 14.1.1). 10. **Part 1, Part 2,and Part 3 (paclitaxel only and PLX3397 + paclitaxel arms):** Paclitaxel premedication administration (recommended, but not required. Investigator should follow standard institutional policies). **11. Part 1, Part 2,and Part 3 (paclitaxel only and PLX3397 + paclitaxel arms):** Paclitaxel administration.	To update study procedures to include Part 3 procedures
13.5 Pre-treatment Cycle 1 Day 15	1. Pre-PLX3397 dose blood sample for PK (**Part 1 only**)	• Pre-PLX3397 dose blood sample for PK (**Part 1 and Part 3 only**) **8. Part 3 only: Pre-PLX3397 dose whole**	To update study procedures to include Part 3 procedures

Section	Amendment 5	Amendment 6	Rationale
		blood sample collection for MDSC **9. Part 3 only: Pre-PLX3397 dose blood for plasma PK and biomarkers**	
13.6 Post-treatment Cycle 1 Day 15 (±48 hours)	Following receipt of all study drugs, patients will undergo the following: 1. Post-dose blood sample for PK (Part 1 only) at 2 and 4 hours following PLX3397 administration 2. AE monitoring	Following receipt of all study drugs, patients will undergo the following: 1. Post-dose blood sample for PK (Part 1 only) at 2 and 4 hours following PLX3397 administration **2. Post-dose blood sample for PK (Part 3 only) at 2, 4, and 6 hours following PLX3397 administration** ~~2.~~3. AE monitoring	To update study procedures to include Part 3 procedures
13.8 Part 3 Only: Cycle 1 Day 28 ± 7 days (Cycle 1 Day 21 to Cycle 1 Day 35)	*Amendment 5 does not contain this section.*	**13.8 Part 3 Only: Cycle 1 Day 28 ± 7 days (Cycle 1 Day 21 to Cycle 1 Day 35)** • **Cancer tissue [2-3 core biopsies of target (≥2 cm diameter) or non-target lesions] for biomarkers**	To update study procedures to include Part 3 procedures
13.9 (Previously 13.8) All Subsequent Cycles, Day 1	7. Blood sample for plasma PK (**Part 1 only**) and PD biomarker analyses taken prior to PLX3397 dose	7. Blood sample for plasma PK (**Part 1 and Part 3 only**) and PD biomarker analyses taken prior to PLX3397 dose 8. **Part 3 only: CA-125 sampling**	To update study procedures to include Part 3 procedures
13.12 (Previously 13.11) End of Study	9. Imaging for tumor assessments	**8. Part 3 only: Blood for plasma PK and biomarkers** **9. Part 3 only: CA-125 sampling** ~~9.~~ 11~~. Imaging for tumor assessments~~ **End of Study imaging for tumor assessments should be obtained for patients who go off study for reasons other than radiographic disease progression**	To update study procedures to include Part 3 procedures

Section	Amendment 5	Amendment 6	Rationale
13.13 (Previously 13.12) Dose-Limiting Toxicities (Part 1 Only)	Non-hematologic DLTs Any CTCAEv4 Grade ≥3 non-hematologic toxicity, **unless the event is clearly unrelated** to treatment with PLX3397 in combination with weekly standard fixed dosing of paclitaxel EXCEPT the following	~~Non-hematologic~~ **Other** DLTs Any CTCAEv4 Grade ≥3 ~~non-hematologic~~ **other** toxicity, **unless the event is clearly unrelated** to treatment with PLX3397 in combination with weekly standard fixed dosing of paclitaxel EXCEPT the following:	To standardize definition of any DLT that is not otherwise discreetly defined
13.14.1 (Previously 13.14) PLX3397 Dose Modifications	During **Part 2**: PLX3397 dose reductions or interruptions for adverse events may take place at any time. For **Part 1** and **Part 2** guidelines for dosage modification for PLX3397–related toxicities as well as guidelines for their management are noted in Table 3.	During **Part 2 and Part 3**: PLX3397 dose reductions or interruptions for adverse events may take place at any time. For **Part 1** ~~and~~ **Part 2, and Part 3,** guidelines for dosage modification for PLX3397–related toxicities as well as guidelines for their management are noted in Table 3.	To add Part 3 to dose modifications.
13.14.1 (Previously 13.14) PLX3397 Dose Modifications	Table 3	Replace Table 3	To update dose modification rules for toxicity and apply uniformity across studies.
13.14.2 (Previously 13.15) Paclitaxel Dose Modifications	For **Part 1, Cycle 2 and subsequent cycles** and **Part 2**, other dose modifications for paclitaxel will be in accordance to the product label.	For **Part 1, Cycle 2 and subsequent cycles** and **for Part 2 and Part 3,** other dose modifications for paclitaxel will be in accordance ~~to~~ **with** the product label.	To add Part 3 to dose modifications.
16.0 SAFETY EVALUATION	*Amendment 5 does not contain Part 3 for this section.*	**For Part 3 only: AE and SAE reporting will commence when the 2-3 core biopsies are obtained during Screening.**	To add start of AE collection for Part 3 of the study
16.1 Physical Examination	Physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at Screening and at all time points indicated in the Trial Flow Chart.	Physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at Screening and at all time points indicated in the Trial Flow Chart. **Photography may be included as part of the physical exam for those patients who consent to the procedure.**	To add option for photography during physical examination
18.0 PHARMACO-KINETIC	18.0 PHARMACOKINETIC EVALUATION (PART 1 ONLY)	18.0 PHARMACOKINETIC EVALUATION (PART 1 ~~ONLY~~ **AND PART 3**)	To add Part 3 to PK evaluation

Section	Amendment 5	Amendment 6	Rationale
EVALUATION			
19.4 Pharmacokinetic Analysis	19.4 Pharmacokinetic Analysis (Part 1 only)	19.4 Pharmacokinetic Analysis (Part 1 ~~only~~ **and Part 3)**	To add Part 3 to PK evaluation
21.1 Definitions	Relatedness to study medication will be graded as either "probably", "possibly", or "unlikely", as follows:	Relatedness to study medication will be graded as either "probably", "possibly", or "~~unlikely~~ **not related**", as follows:	To align with the specified definitions listed
21.2 Recording and Reporting	A patient's AE or SAE can occur from the time the patient receives the first dose of study drug up to 28 days after the last dose and prior to starting another therapy.	A patient's AE or SAE can occur from the time the patient receives the first dose of study drug up to 28 days after the last dose and prior to starting another therapy**. For Part 3 only, AE and SAE reporting will commence when the 2-3 core biopsies are obtained during Screening.**	To add start of AE collection for Part 3 of the study
21.3 Serious Adverse Event Reporting	All SAEs, other reportable information, and follow-up information must be reported within 24 hours of learning of the event by completing the SAE eCRF TEMPO.	All SAEs, other reportable information, and follow-up information must be reported within 24 hours of learning of the event by completing the SAE eCRF in **the electronic data capture system** ~~TEMPO.~~	To allow for SAEs to be reported in an electronic data capture system other than TEMPO
26.2 Sponsor	Data are checked as they are entered into the electronic data capture system (TEMPO).	Data are checked as they are entered into the ~~electronic data capture system~~ **EDC** ~~(TEMPO).~~	To allow for data to be entered in an electronic data capture system other than TEMPO
29.0 REFERENCES	*All references*	*Update to full citation*	To give full and correct citation for all references
29.0 REFERENCES	*Amendment 5 does not contain these references*	Chambers SK, Kacinski BM, Ivins CM, Carcangiu ML. Overexpression of epithelial macrophage colony-stimulating factor (CSF-1) and CSF-1 receptor: a poor prognostic factor in epithelial ovarian cancer, contrasted with a protective effect of stromal CSF-1. Clin Cancer Res. 1997;3(6):999–1007. Kacinski BM, Scata KA, Carter D, Yee LD, Sapi E, King BL, et al. FMS (CSF-1 receptor) and CSF-1 transcripts and protein are expressed by human breast carcinomas in vivo and in vitro. Oncogene. 1991;6(6):941–952.	To include new references used in Section 7.0

Section	Amendment 5	Amendment 6	Rationale
		Kacinski BM, Stanley ER, Carter D, Chambers JT, Chambers SK, Kohorn EI, et al. Circulating levels of CSF-1 (M-CSF) a lymphohematopoietic cytokine may be a useful marker of disease status in patients with malignant ovarian neoplasms. Int J Radiat Oncol Biol Phys. 1989;17(1):159–164. Price FV, Chambers SK, Chambers JT, Carcangiu ML, Schwartz PE, Kohorn EI, et al. Colony-stimulating factor-1 in primary ascites of ovarian cancer is a significant predictor of survival. Am J Obstet Gynecol. 1993;168(2):520–527. Ruffell B, Coussens LM. Macrophages and therapeutic resistance in cancer. Cancer Cell. 2015;27(4):462–472. Scholl SM, Bascou CH, Mosseri V, Olivares R, Magdelenat H, Dorval T, et al. Circulating levels of colony-stimulating factor 1 as a prognostic indicator in 82 patients with epithelial ovarian cancer. Br J Cancer. 1994;62(2):342–346. Skates SJ, Horick N, Yu Y, Xu FJ, Berchuck A, Havrilesky LJ, et al. Preoperative sensitivity and specificity for early-stage ovarian cancer when combining cancer antigen CA-125II, CA 15-3, CA 72-4, and macrophage colony-stimulating factor using mixtures of multivariate normal distributions. J Clin Oncol. 2004;22(20):4059–4066. Toy EP, Chambers JT, Kacinski BM, Flick MB, Chambers SK. The activated macrophage colony stimulating factor (CSF-1) receptor as a predictor of poor outcome in advanced epithelial ovarian carcinoma. Gynecol Oncol. 2001;80(2):194–200. Zhang Z, Yu Y, Xu F, Berchuck A, van Haaften-Day C, Havrilesky LJ, et al. Combining multiple	

Section	Amendment 5	Amendment 6	Rationale
		serum tumor markers improves detection of stage I epithelial ovarian cancer. Gynecol Oncol. 2007;107(3):526–531.	
ATTACHMENT 1: Laboratory Tests	**Blood Response Biomarkers (samples):** • CSF-1 • CD14/CD16 positive monocytes (Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, a definitive list of analyses remains to be determined.)	**Part 1, Part 2, and Part 3:** **Blood Response Biomarkers (samples):** • CSF-1 • CD14/CD16 positive monocytes (Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, a definitive list of analyses remains to be determined.) **Part 3:** **Cancer tissue biomarkers will include:** • **IHC for CD68, CD8, PD-L1, and additional markers of macrophage and T-cell presence and function** • **RNA expression analysis for an exploratory panel of tumor microenvironment markers** • **Staining of cells of the tumor microenvironment. Panels of IHC markers specific for macrophages, T-cells, and other immune and inflammatory cells will be employed, for semi-quantitative changes in cell number, location within the tumor, and degree of activation.** **Blood biomarkers will include:** • **CA-125 sampling requirements: 2 pre-treatment samples, first sample within 3 months of starting therapy and second sample within 1 week of Cycle 1 Day 1; subsequent samples on the first day of each cycle starting with**	To include sampling for Part 3

Section	Amendment 5	Amendment 6	Rationale
		Cycle 2 Day 1 and End-of-Study Visit. • **Plasma CSF-1 and additional markers of treatment effect** • **Whole blood CD14/CD16 monocyte subset by FACS analysis** • **Whole blood MDSC by FACS analysis**	

ATTACHMENT 11: AMENDMENT 7 SUMMARY OF CHANGES

The following changes were made from Amendment 6 (27 May 2015) to Amendment 7 of the protocol:

- The inclusion criterion was revised to change the duration that patients could be previously treated with a taxane from 1 year to 6 months.

  Rationale: To increase patient enrollment.

- The number of sites enrolling patients in Part 3 of the study was increased from 3-6 sites to approximately 9 sites.

  Rationale: To increase patient enrollment.

- Clarification was added that if a biopsy during Cycle 1 is delayed beyond Day 28, patients will have a Day 28 visit added in Cycle 1 for paclitaxel administration. Visit procedures would be the same as the Day 22 visit.

  Rationale: To provide procedures for a biopsy delay in Cycle 1.

- A section was added in the main body of the protocol to describe study stopping rules (now Section 17.0).

  Rationale: Study stopping rules were previously included in the synopsis but not in the main body of the protocol.

- Protocol text was corrected to remove blood biomarker collection on Cycle 1 Day 21-35.

  Rationale: The study flow chart was correct that only cancer tissue should be obtained on Cycle 1 Day 21-35 and not blood biomarkers.

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

ATTACHMENT 12: AMENDMENT 8 SUMMARY OF CHANGES

- Additional serum chemistry testing was added on Days 8, 15, and 22 for the following:
  - **Cycle 2 only:** serum chemistry required prior to paclitaxel administration for **Part 3 – all arms**.
  - **Cycle 3 only:** serum chemistry required for **Part 3 - Lead-in Paclitaxel Alone Arm** only.

Rationale: To increase monitoring of liver function during the first 8 weeks of PLX3397 therapy due to updated safety information.

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