CLINICAL STUDY PROTOCOL

Protocol Number:	PLX124-03
Title:	A Multicenter, Open-Label, Parallel, Phase 2a Study of PLX2853 Monotherapy in Advanced Gynecological Malignancies with a Known ARID1A Mutation and Phase 1b/2a Study of PLX2853/Carboplatin Combination Therapy in Platinum-Resistant Epithelial Ovarian Cancer
Indication:	Advanced gynecological malignancies with a known ARID1A mutation and platinum-resistant epithelial ovarian cancer
Phase:	2a (PLX2853 monotherapy), 1b/2a (PLX2853 + carboplatin)
Sponsor:	Plexxikon Inc. 329 Oyster Point Boulevard South San Francisco, CA 94080, USA Telephone: (510) 647-4000
IND Number:	147,651
EudraCT Number:	Not Applicable
Therapeutic Area:	Antineoplastic Agent
Medical Monitor:	Athanasios Tsiatis, MD Telephone: (510) 647-4142 Mobile: (510) 590-6443 Email: atsiatis@plexxikon.com
Protocol History:	
Date/Version:	16 April 2020/Original 29 May 2020/Amendment 1 03 May 2021/Amendment 2

SPONSOR SIGNATURE

Protocol PLX124-03:	A Multicenter, Open-Label, Parallel, Phase 2a Study of PLX2853 Monotherapy in Advanced Gynecological Malignancies with a Known ARID1A Mutation and Phase 1b/2a Study of PLX2853/Carboplatin Combination Therapy in Platinum-Resistant Epithelial Ovarian Cancer
Sponsor:	Plexxikon Inc. 329 Oyster Point Boulevard South San Francisco, CA 94080, USA Telephone: (510) 647-4000

I have read and approved this protocol.

INVESTIGATOR AGREEMENT AND SIGNATURE

Protocol PLX124-03:	A Multicenter, Open-Label, Parallel, Phase 2a Study of PLX2853 Monotherapy in Advanced Gynecological Malignancies with a Known ARID1A Mutation and Phase 1b/2a Study of PLX2853/Carboplatin Combination Therapy in Platinum-Resistant Epithelial Ovarian Cancer
Sponsor:	Plexxikon Inc. 329 Oyster Point Boulevard South San Francisco, CA 94080, USA Telephone: (510) 647-4000

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 Council on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations, and the ethical principles that have their origins in the Declaration of Helsinki. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

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

Principal Investigator Signature	Date

Principal Investigator Name and Title (print)

Investigational site or name of institution and location (printed)

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

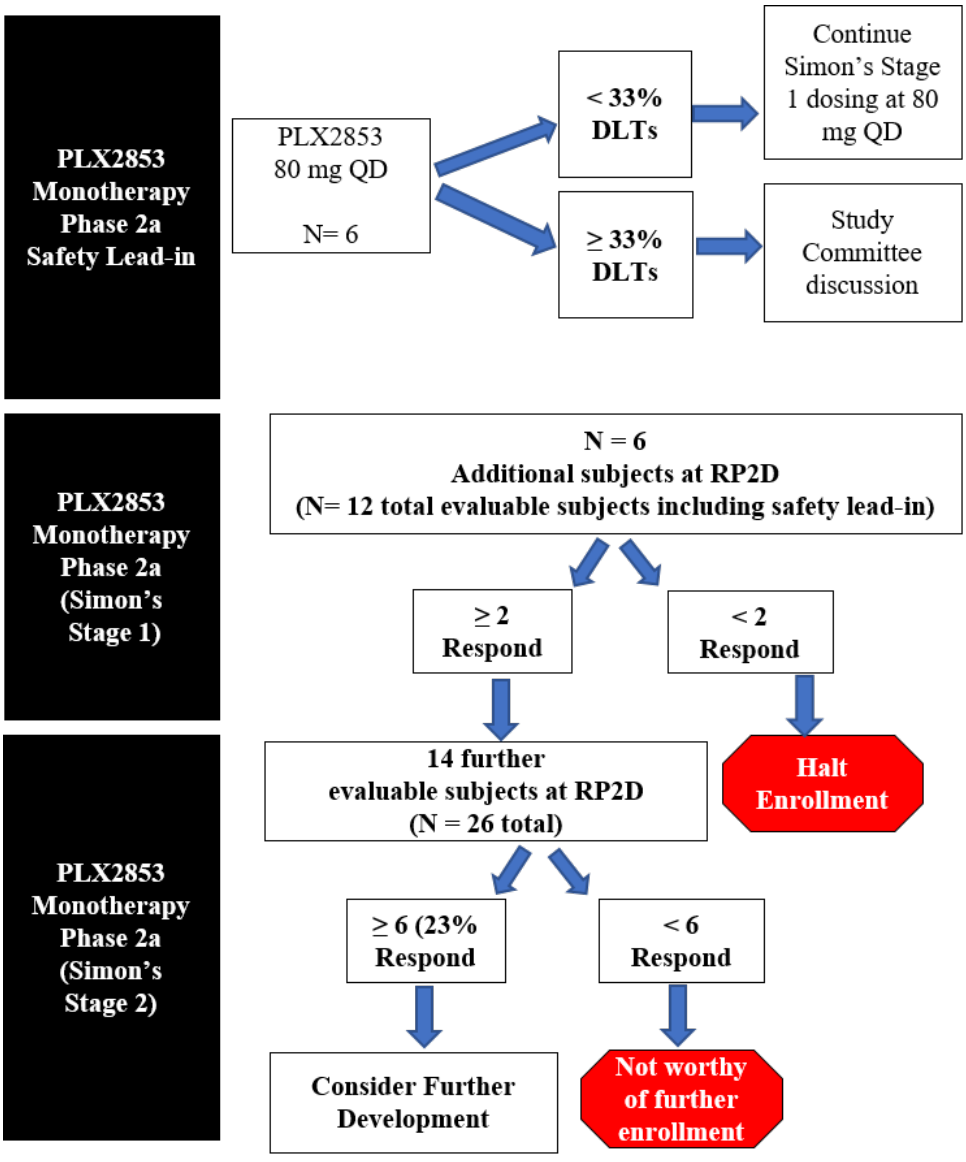
Abbreviation or Term	Definition/Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero extrapolated to infinite time
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours postdose
AUC_{0-last}	area under the concentration-time curve from time zero to time of last observed concentration hours postdose
BCRP	breast cancer resistance protein
BDC	bile duct-cannulated
BID	twice daily
BET	bromodomain and extra terminal domain
BRD	bromodomain-containing protein
CA-125	cancer antigen 125
CI	confidence interval
CI_{90}	90% confidence interval
CL	clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed concentration
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOC	epithelial ovarian cancer
ESI+	electrospray ionization in positive ion mode
FU	follow-up

Abbreviation or Term	Definition/Explanation
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HGSOC	high-grade serous ovarian cancer
HNSTD	highest non-severely toxic dose
HPLC	high performance liquid chromatography
HRD	homologous recombination deficiency
IBW	ideal body weight
IC	inhibitory concentration
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous, intravenously
K_d	dissociation constant
LC/MS/MS	liquid chromatography tandem mass spectrometry
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NGS	next generation sequencing
NOAEL	no-observed-adverse-effect level
NRG1	neuregulin-1
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCCC	ovarian clear cell carcinoma
ORR	overall response rate
OS	overall survival
PARP	poly-(ADP-ribose) polymerase
PD	progressive disease
PDx	pharmacodynamic
PFS	progression-free survival
PG	pharmacogenomics
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
QD	once daily

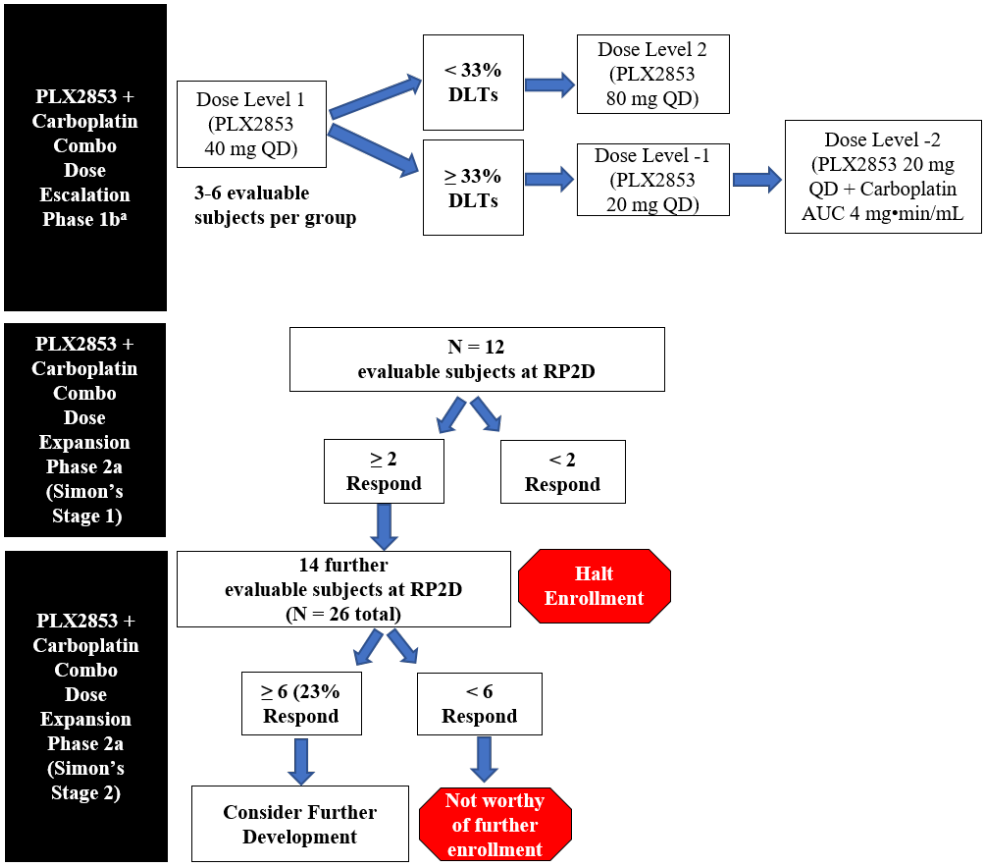
Abbreviation or Term	Definition/Explanation
QD-5/2	5-day on, 2-day off intermittent dosing
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's equation
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SWI/SNF	switch/sucrose non-fermentable
$T_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T_{max}	time to maximum observed concentration
ULN	upper limit of normal
US	United States
UV	ultraviolet

PROTOCOL SYNOPSIS

Title:	A Multicenter, Open-Label, Parallel, Phase 2a Study of PLX2853 Monotherapy in Advanced Gynecological Malignancies with a Known ARID1A Mutation and Phase 1b/2a Study of PLX2853/Carboplatin Combination Therapy in Platinum-Resistant Epithelial Ovarian Cancer
Sponsor:	Plexxikon Inc.
Clinical Phase:	Phase 2a (PLX2853 monotherapy), Phase 1b/2a (PLX2853 + carboplatin)
Indications:	• Advanced gynecological malignancies with a known ARID1A mutation (with and without PIK3CA, PIK3R1, and/or PTEN mutations) • Platinum-resistant epithelial ovarian cancer (EOC) (including fallopian tube or primary peritoneal cancer)
Objectives:	**Phase 2a (PLX2853 monotherapy)** Primary objective: • To evaluate the efficacy of single-agent PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation Secondary objectives: • To further characterize the safety and efficacy of single-agent PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation • To further evaluate the pharmacokinetics (PK) of PLX2853 **Phase 1b (PLX2853 + carboplatin combination)** Primary objective: • To evaluate the safety and tolerability of PLX2853 + carboplatin combination including dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) in subjects with platinum-resistant EOC Secondary objective: • To characterize the PK and efficacy of PLX2853 when combined with carboplatin in subjects with platinum-resistant EOC **Phase 2a (PLX2853 + carboplatin combination)** Primary objective: • To evaluate the efficacy of PLX2853 + carboplatin combination at the RP2D in subjects with platinum-resistant EOC Secondary objective: • To further characterize the safety and PK of PLX2853 when combined with carboplatin in subjects with platinum-resistant EOC **All Phases** Exploratory objectives: • To assess biomarkers in peripheral blood cells, tumor cells, and tissue biopsies • To further evaluate the pharmacodynamics (PDx) of PLX2853

Study Design:	This open-label, multicenter, 2-part study will evaluate in parallel PLX2853 monotherapy in subjects with advanced gynecological malignancies with a known ARID1A mutation (with and without PIK3CA, PIK3R1, and/or PTEN mutations) and PLX2853 and carboplatin combination therapy in subjects with platinum-resistant EOC (including fallopian tube or primary peritoneal cancer). The study schema and study design are presented below. **PLX2853 Monotherapy Study Design:** 

PLX2853 + Carboplatin Combination Study Design:



[a] All carboplatin doses are target AUC of 5 mg•min/mL unless otherwise specified.
Note: Alternative scheduling of PLX2853 administration may be evaluated.

Phase 2a (PLX2853 Monotherapy)

The Phase 2a monotherapy part will evaluate the efficacy, safety, PK, and PDx of PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation using a Simon's 2-stage design. ARID1A, PIK3CA, PIK3R1, PTEN, and homologous recombination repair mutational status and homologous recombination deficiency status will be determined based on historical data for all potential subjects from a commercially available next generation sequencing (NGS) panel such as FoundationOne® CDx or a local NGS panel performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.

The safety lead-in will comprise of 6 subjects who will be enrolled at a dose of 80 mg/day and assessed for safety by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and for evidence of DLTs. The rules for determining DLT are defined further below. After the safety lead-in has been completed, the Study Committee will convene to evaluate safety, PK, and PDx data to determine which dose to take forward for the remainder of subjects in Phase 2. Response rate for subjects in the safety lead-in will be included in the efficacy analysis for the purpose of the Simon's 2 stage design.

The starting dose level of PLX2853 will be 80 mg/day. In the absence of a DLT and in conjunction with review of the PK and PD data from each cohort by the Study Committee, the safety lead-in is planned to occur in the following manner:

- The starting dose of PLX2853 will be 80 mg/day

	• DLTs will be assessed in the first 28-day treatment period/cycle After dosing has been completed in this cohort of subjects, safety, PK, and PDx data (as applicable) will be reviewed, and any dose modification decisions, if applicable, will be made by the Study Committee. If ≥33% DLTs are seen during the initial safety lead-in, the Safety Committee will convene to consider a dose reduction. If a dose reduction is deemed appropriate, the subjects in the initial safety lead-in will need to be replaced and a repeat 6 subject safety lead-in will need to be conducted at this lower dose. Dose modification decisions will also take into consideration safety information beyond the DLT period from all enrolled subjects. If no DLT is observed, the recommended dose for further evaluation may be established based on safety, PK, and PDx convenience of dosing in subjects treated at that dose. If a DLT is seen in ≥33% of subjects in the safety lead-in then the Study Committee will convene to consider alternative dose levels and schedule. In order to be DLT evaluable a subject must not have missed more than 25% of study drug for reasons other than an adverse event (AE) and must not have missed receiving carboplatin within 7 days of Cycle 2 Day 1 (if applicable) for reason other than AE. If a subject misses more than 25% of the doses for Cycle 1 (e.g., >7 doses of PLX2853 in 28 days) during the DLT window period for reasons other than an AE, additional subject(s) may be enrolled to provide adequate data for safety assessments. PLX2853 PK data will be analyzed for peak concentration (C_{max}), area under the plasma concentration–time curve (AUC), and accumulation ratio at steady state and compared with prior dose levels. Dose adjustments may also require increasing the number of subjects at a given dose level as a result of the review of safety, observed or anticipated disease activity, and PK data. A subset of patients may be studied in the monotherapy part of this trial to assess the effect of food on PLX2853 exposure. These subjects will receive a single dose of PLX2853 under fed conditions 3 or 4 days prior to Cycle 1 Day 1 and have serial PK samples collected. On Cycle 1 Day 1, subjects will commence dosing at the same dose level under fasted conditions. At the discretion of the Sponsor, an additional Phase 2a monotherapy cohort may be enrolled using a Simon's 2 stage design to evaluate the efficacy, safety, PK, and PDx of PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation and who do not have known pathogenic mutations in the following genes (unless allowed with Medical Monitor approval): • Mutations or amplifications in PIK3CA • Mutations or amplifications in PIK3R1 • Mutations or deletions in PTEN **Phase 1b/2a (PLX2853 + Carboplatin Combination)** The Phase 1b/2a combination part of the study will evaluate the safety, PK, PDx, and efficacy of PLX2853 in combination with carboplatin in subjects with platinum-resistant EOC. In Phase 1b (dose escalation), the safety profile, RP2D/MTD, PK, PDx, and preliminary efficacy of PLX2853 (administered orally in 28-day treatment cycles) in combination with carboplatin (administered intravenously on Day 1 of each 28-day cycle) will be evaluated. Each cohort will be enrolled and assessed using a standard "3+3" design. The rules for determining DLTs and dose escalation are defined further below.

The provisional dose escalation plan is detailed as follows:

Dose Level	Combination PLX2853 Dose (mg/day)[a]	Carboplatin Dose (mg•min/mL)[b]
-2	20	AUC 4
-1	20	AUC 5
1 (Starting Dose)	40	AUC 5
2	80	AUC 5

[a] Once daily dosing schedule unless otherwise specified.

[b] Dosed on Day 1 of each 28-day cycle.

In Phase 1b combination, the starting dose level of PLX2853 will be 40 mg/day plus a target AUC of 5 mg•min/mL dose of carboplatin (Cohort 1). In the absence of a DLT in the first cycle of treatment and in conjunction with review of the PK and available PDx data from each cohort by the Study Committee, dose escalation is planned to occur in the following manner:

- DLTs will be assessed in the first treatment cycle (up to carboplatin dosing on Cycle 2 Day 1).
- The starting dose of PLX2853 will be 40 mg/day (Cohort 1), which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day.
- Carboplatin will be administered using a target AUC of 5 mg•min/mL on Day 1 of each 28-day treatment cycle per label. Carboplatin must be given within 7 days of Cycle 2 Day 1 (delays due to reasons other than toxicity will not be assessed as a DLT).
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be investigated. If that dose level is intolerable, Dose Level -2 (PLX2853 20 mg/day and carboplatin AUC 4 mg•min/mL) will be studied. If that dose level is intolerable, the study will be halted.
- In the absence of a DLT, a second cohort with a PLX2853 dose of 80 mg/day will be investigated (Cohort 2).

A minimum of 3 to 4 subjects will be initially enrolled in Cohort 1. If a DLT is observed in 1 subject in a given cohort, up to 6 subjects will be treated at that dose. If DLTs are observed in 2 or more of 6 subjects (or ≥33% of the cohort) at a dose level, the dose at which this occurs will be considered intolerable and the MTD will have been exceeded. The highest dose level at which 0 of 3 subjects or 0 or 1 of 6 subjects experience a DLT will be declared the RP2D. If 3 to 4 subjects were initially evaluated at that dose level, an additional 2 to 3 subjects may be enrolled to evaluate for DLTs at that dose level for confirmation. Up to 6 additional subjects with a known ARID1A mutation (unless otherwise approved by the Medical Monitor) may be treated at the RP2D at the discretion of the Sponsor for dose confirmation purposes.

In order to be DLT evaluable a subject must not have missed more than 25% of study drug for reasons other than an AE and must not have missed receiving carboplatin within 7 days of Cycle 2 Day 1 (if applicable) for reason other than an AE. If a subject misses more than 25% of the doses for Cycle 1 (e.g., >7 doses of PLX2853 in 28 days) during the DLT window for reasons other than an AE, additional subject(s) may be enrolled to provide adequate data for dose escalation decision making. Subjects who do not complete Cycle 1 for reasons other than drug toxicity may be replaced. Subjects must receive their Cycle 2 Day 1 carboplatin dose to be considered evaluable unless the reason for missing carboplatin is due to an AE.

Once all ongoing subjects in a dose cohort have been treated for at least 2 cycles and the safety and tolerability of that dose level has been established, intra-subject dose escalation to that dose level may be permitted for subjects enrolled at lower dose levels who have not experienced an unresolved Grade 3 or higher treatment-related toxicity and have completed

	2 cycles. Any intra-subject dose escalation requires a discussion and agreement with the Medical Monitor. After dosing has been completed in each cohort, safety, PK, and PDx data (if available) will be reviewed, and dose escalation decisions will be made by the Study Committee. Dose escalation decisions will also take into consideration safety information beyond the DLT period from earlier cohorts. If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, convenience of dosing, and PDx (if available) in subjects treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days. PLX2853 and carboplatin may not be dose escalated in the same cycle. PLX2853 PK data will be analyzed in each dosing cohort for C_{max}, AUC, and accumulation ratio at steady state and compared with prior dose levels. The number of subjects at a given dose level may be increased as a result of the review of safety, observed or anticipated disease activity, and PK data. Additional dosing schedules may be studied, such as alternate day dosing (e.g., every other day) depending on emerging safety and PK data. In Phase 2a (dose expansion), efficacy as well as additional safety, PK, and PDx data of PLX2853 in combination with carboplatin at the RP2D dose established in Phase 1b by the Study Committee will be obtained using a Simon's 2-stage design.
Number of Subjects:	Total number of subjects: up to 85 evaluable subjects **Phase 2a (PLX2853 monotherapy): Up to 38 evaluable subjects** There will be up to 2 Simon's 2-stage design cohort of up to 38 evaluable subjects with ARID1A mutation-positive (with and without PIK3CA, PIK3R1, and/or PTEN mutations) advanced gynecological malignancies. The safety lead-in of 6 subjects dosed at the level selected for Phase 2a will be included in the group of 12 evaluable subjects for Stage 1. **Phase 1b (PLX2853 + carboplatin combination): Up to 21 evaluable subjects** Approximately 9 to 15 evaluable subjects with platinum-resistant EOC will be enrolled, depending on the number of escalation cohorts investigated. Up to 6 additional subjects with a known ARID1A mutation (unless otherwise approved by the Medical Monitor) may be treated at the RP2D at the discretion of the Sponsor for dose confirmation purposes. **Phase 2a (PLX2853 + carboplatin combination): Up to 26 evaluable subjects** There will be 1 Simon's 2-stage design cohort of between 12 to 26 evaluable subjects with platinum-resistant EOC.
Inclusion Criteria:	1. Age ≥18 years at the time of signing informed consent 2. Histologically or cytologically confirmed diagnosis of 1 of the following, and must have measurable disease per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1): • **Phase 2a (PLX2853 monotherapy)**: Any advanced gynecological malignancy (cervical, vaginal, vulvar, uterine, ovarian, fallopian tube, or primary peritoneal) with a known ARID1A mutation, that is intolerant to or refractory to all standard therapy known to confer clinical benefit. • Subjects must have tumor accessible for sequential biopsy and be willing to provide on-study tumor tissue biopsy (core needle biopsy or excision required). Tissue collection must not constitute a significant risk procedure. A significant risk procedure is generally considered to be one for which the procedure associated absolute risk of mortality or major morbidity in the patient's clinical setting and at the institution completing the procedure is 2% or higher. When possible, newly obtained tissue should be collected from a non-target lesion. • **Phase 1b and Phase 2a (PLX2853 + carboplatin combination):** Platinum-resistant EOC (including fallopian tube or primary peritoneal cancer). Platinum-resistant is defined as disease that may have responded to a platinum-containing chemotherapy

regimen, but there is documentation of demonstrated recurrence within 6 months following the completion of that platinum-containing regimen.

OR

Subjects with platinum-refractory EOC are eligible, provided refractory outcome was to second line or later repeated platinum regimen (not first line). Refractory is defined as disease that failed to achieve at least a partial response (PR) to a platinum-containing regimen (i.e., stable disease [SD] or actual disease progression).

Progressive disease (PD) of EOC following platinum-based therapy can be documented by physical examination, computed tomography (CT) scans, or a doubling of cancer antigen 125 (CA-125) levels from either 1) upper limit of normal (ULN) or 2) most recent nadir value (per the Rustin criteria [Rustin 2011] [Appendix 6]). For CA-125 to be used as a criterion for PD, the CA-125 level nadir must have been above the ULN. In addition, the CA-125 nadir level must have been confirmed by a second measurement at least 1 week after the initial measurement.

- Subjects in Phase 2a must have tumor accessible for sequential biopsy and be willing to provide on-study tumor tissue biopsy (core needle biopsy or excision required). Tissue collection must not constitute a significant risk procedure. A significant risk procedure is generally considered to be one for which the procedure associated absolute risk of mortality or major morbidity in the patient's clinical setting and at the institution completing the procedure is 2% or higher. When possible, newly obtained tissue should be collected from a non-target lesion.

3. Eastern Cooperative Oncology Group Performance Status 0 to 1
4. Adequate organ function as demonstrated by the following laboratory values. All Screening laboratory tests should be performed within 10 days of the first PLX2853 dose. Subjects must meet the following eligibility criteria prior to dosing:

- Hematological:
  - Neutrophils ≥1500/µL
  - Platelets ≥100,000/µL
  - Hemoglobin ≥9 g/dL (transfusion and erythropoietin not permitted within 14 days prior to blood draw)
- Renal:
  - Estimated glomerular filtration rate (GFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine calculation [Appendix 1]) ≥60 mL/min/1.73 m^2
- Hepatic:
  - Serum total bilirubin ≤1.5 × ULN

    OR
  - Direct bilirubin ≤ULN for subjects with total bilirubin >1.5 × ULN

    Exception for elevated bilirubin secondary to Gilbert's disease, in which case it must be ≤2.5 mg/dL. Confirmation of Gilbert's diagnosis requires: elevated unconjugated (indirect) bilirubin values; normal complete blood count in previous 12 months, blood smear, and reticulocyte count; normal aminotransferases and alkaline phosphatase in previous 12 months
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN
  - Gamma-glutamyl transferase ≤3 × ULN
- Coagulation:

	– International normalized ratio ≤1.5 × ULN – Activated partial thromboplastin time ≤1.5 × ULN • Chemistry: – Albumin ≥3.0 g/dL 5. Women of child bearing potential (defined as any female who has experienced menarche and who has not undergone successful surgical sterilization [hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or is not postmenopausal) must have a negative serum pregnancy test within 7 days prior to taking the first dose of study drug and, if sexually active, must agree to use a highly effective method of contraception (a contraception method with a failure rate <1% per year) and 1 additional barrier method from the time of the negative pregnancy test to 90 days (for subjects in the United States) or 6 months (for subjects in Canada) after the last dose of study drug. Women of non-child bearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. 6. Except as specified above for organ function, all drug-related toxicity from previous cancer therapy must be resolved (to Grade ≤1 or baseline per NCI CTCAE version 5.0) prior to study treatment administration (Grade 2: alopecia, hot flashes, decreased libido, immune-oncology drug induced hypothyroidism controlled with medication, or neuropathy is allowed). 7. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements
Exclusion Criteria:	1. Prior exposure to a bromodomain inhibitor, such as OTX-015 or CPI-0610 2. Ongoing systemic infection requiring treatment with antibiotic, antiviral, or antifungal treatment 3. Autoimmune hemolytic anemia or autoimmune thrombocytopenia 4. Presence of symptomatic or uncontrolled central nervous system or leptomeningeal metastases (Note: Subjects with stable, treated brain metastases are eligible for this study. However, subjects must not have required steroid treatment for their brain metastases within 30 days of Screening.) 5. Red blood cell or platelet transfusion within 14 days of Screening blood draw 6. Known or suspected allergy to the investigational agent or any agent given in association with this study 7. Use of biotin (i.e., Vitamin B7) or supplements containing biotin higher than the daily adequate intake of 30 µg (NIH-ODS 2020). (Note: Subjects who switch from a high dose to a dose of 30 µg/day or less are eligible for study entry.) Use of herbal, alternative, and food supplements (i.e., PC-Spes, Saw Palmetto, St. John's Wort, etc.) and probiotics must be discontinued before treatment start. Daily multi-vitamin (provided it does not contain biotin >30 µg/day), calcium, and Vitamin D are permitted. 8. Use of strong inhibitors and inducers of CYP3A4 and 2C8 (Appendix 2) 9. Clinically significant cardiac disease, defined as any of the following: • Clinically significant cardiac arrhythmias including bradyarrhythmias and/or subjects who require anti-arrhythmic therapy (excluding beta blockers or digoxin). Subjects with controlled atrial fibrillation are not excluded. • Congenital long QT syndrome or subjects taking concomitant medications known to prolong the QT interval (drugs with a low risk of QTc prolongation that are needed for infection control or nausea may be permitted with approval from the Medical Monitor). A list of drugs known to prolong the QT interval and risk of Torsades de pointes can be found in Appendix 4. • QT interval corrected using Fridericia's equation (QTcF) ≥470 msec at Screening (based on average of triplicate electrocardiograms (ECGs) at baseline)

	• If the QTc is prolonged in a subject with a pacemaker or bundle branch block, the subject may be enrolled in the study if confirmed by the Medical Monitor • History of clinically significant cardiac disease or congestive heart failure >New York Heart Association Class II. Subjects must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months. • Uncontrolled hypertension, defined as systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg that has been confirmed by 2 successive measurements despite optimal medical management • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within the 3 months before start of study medication (except for adequately treated catheter-related venous thrombosis occurring >1 month before the start of study medication) 10. Inability to take oral medication or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the Investigator, would preclude adequate absorption 11. Poorly controlled known Type 2 diabetes with HbA1C >7.5% 12. Non-healing wound, ulcer, or bone fracture 13. Infection with HIV-1 or HIV-2. **Exception:** subjects with well-controlled HIV (e.g., CD4 >350/mm^3 and undetectable viral load) are eligible. 14. Current active liver disease from any cause, including hepatitis A (hepatitis A virus immunoglobulin M positive), hepatitis B (hepatitis B virus [HBV] surface antigen positive), or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid). Subjects with HCV with undetectable virus after treatment are eligible. Subjects with a prior history of HBV are eligible if quantitative PCR for HBV DNA is negative. Note that elevated levels of biotin may interfere with viral serology testing. 15. Active known second malignancy with the exception of any of the following: • Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer • Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥2 years • Any other cancer from which the subject has been disease-free for ≥3 years 16. Major surgery or significant traumatic injury within 28 days prior to Cycle 1 Day 1 17. Hospitalization for subacute bowel obstruction within 28 days prior to Cycle 1 Day 1 18. Receipt of anti-cancer therapy prior to Cycle 1 Day 1: • Chemotherapy, radiation therapy, or small molecule anti-cancer therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) of Cycle 1 Day 1 • Immune therapy or other biologic therapy (e.g., monoclonal antibodies, antibody-drug conjugates) for the treatment of cancer within 21 days or 5 half-lives (whichever is shorter) of Cycle 1 Day 1 Subjects can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 28 days prior to treatment with study drug. 19. Subject is participating in any other therapeutic clinical study (observational or registry studies are allowed) 20. Subjects who are pregnant or breast-feeding

	21. Presence of any other medical, psychological, familial, sociological, or geographic condition potentially hampering compliance with the study protocol or would interfere with the study endpoints or the subject's ability to participate.
Duration of Study:	**Screening:** • Up to 28 days prior to the first dose of study drug **Treatment Period:** • Daily in 28-day treatment cycles until subject discontinuation or withdrawal or study termination • Subjects participating in the optional Food Effect sub-study will take a single dose of PLX2853 3 or 4 days prior to Cycle 1 Day1. • For subjects enrolled in either the monotherapy or combination therapy cohorts, further treatment with either PLX2853 and/or carboplatin will depend on tolerability and clinical benefit as described in Section 7.1.5. In general, for subjects receiving the combination of PLX2853 + carboplatin, it is estimated that subjects will be treated with carboplatin for up to 6 cycles. **30-day Follow-up (FU) Visit:** • Approximately 30 days after the last dose of study drug or prior to starting any new anti-cancer therapy, whichever occurs first. **Long-term Follow-up:** • Subjects will be followed until death, withdrawal of consent, or loss to follow-up according to the following schedule: - First 2 years after the 30-day FU Visit – Every 3 months - Third year after the 30-day FU Visit and beyond – Every 6 months • Survival follow-up can be via clinic visit, phone call to the subject or referring physician, or other method deemed appropriate by the site and should assess survival, progression, subsequent therapy, and response. • Any subject with a confirmed response who discontinues treatment for reasons other than disease progression will continue to be followed per standard of care and no less than every 3 months until documented disease progression, initiation of a new anti-cancer treatment, or 1 year from discontinuation of study treatment. Radiographic scan data will be collected and if scan data are not available, a scan will be obtained every 3 months until 6 months of radiographic follow-up after confirmed response has been obtained.
Test Product, Dose, and Mode of Administration:	PLX2853 is formulated as 20 mg strength tablets for oral use. Subjects should fast for at least 2 hours before and 1 hour after taking PLX2853, except for PK collection days when subjects should fast for at least 8 hours (10 hours on fed dosing day for the optional Food Effect sub-study) before taking PLX2853 and 1 hour (4 hours on fed dosing day for the optional Food Effect sub-study) after taking PLX2853. During the fasting period, subjects may have a low-fat snack (e.g., crackers, dry toast, etc.) if they experience gastrointestinal symptoms (e.g., nausea, vomiting, etc.) following dosing. Doses will be taken orally with water. PLX2853 should be taken at approximately the same time each day. PLX2853 should be swallowed whole and not crushed, chewed, or dissolved in water. A dosing period of up to 30 minutes is permissible if required by the number of tablets to be taken or as convenient for the subject. Carboplatin is supplied as a sterile, pyrogen-free 10 mg/mL aqueous solution of carboplatin, USP for injection. The NCCN 2018 recommendations should be used for carboplatin dosing as follows: The Calvert equation should be applied to calculate dosage using a target AUC in mg•min/mL: Carboplatin dose (mg) = (target AUC) × (GFR + 25)

	Target AUC will be 5 mg•min/mL. With the Calvert equation, the total dose of carboplatin is calculated in mg not mg/m^2. The GFR should be estimated by calculated creatinine clearance (CrCl) using the Cockcroft-Gault equation: $\text{CrCl (male; mL/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dL)}}$ CrCl (female; mL/min) = 0.85 × CrCl (male) The dose of carboplatin for desired exposure (AUC) should be capped to avoid potential toxicity due to overdosing. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for subjects with normal renal function. Based on the Calvert equation, the maximum doses can be calculated as follows: Maximum carboplatin dose (mg) = Target AUC (mg•min/mL) × (125 mL/min + 25) For a target AUC = 5, the maximum dose is 5 × 150 = 750 mg For a target AUC = 4, the maximum dose is 4 × 150 = 600 mg For overweight or obese subjects (body mass index ≥25 kg/m^2), consider using an adjusted body weight: Adjusted body weight (kg) = ideal body weight (IBW) + 0.4 × (total body weight – IBW) For subjects with abnormally low serum creatinine, including elderly or cachectic subjects, consider using a minimum creatinine of 0.7 mg/dL to avoid overestimation of CrCl. Once the initial dose of carboplatin is calculated, it does not need to be recalculated for subsequent cycles unless the subject is experiencing toxicity and requires dose modification to a lower dose of carboplatin.

Definition of Dose-limiting Toxicity (DLT)	DLTs are defined as clinically significant AEs or laboratory abnormalities occurring during the first cycle of study drug administration that are *at least possibly related* to either PLX2853 or carboplatin and clearly unrelated to disease progression, concurrent illness, or concomitant medication, and that meet one of the following CTCAE v5.0 criteria below. DLTs will be evaluated for the monotherapy safety lead-in subjects as well as each Phase 1b (PLX2853 + carboplatin) escalation cohort. Toxicities occurring in treatment Cycle 2 or later will be reviewed and their impact on subsequent dosing levels and frequency assessed.
	In Phase 1b (PLX2853 + carboplatin), there will be a 24-hour delay between the first and subsequent subjects enrolled in each dose escalation cohort to maximize the safety of enrolled subjects.
	Subjects participating in the optional Food Effect sub-study as well as the monotherapy safety lead-in will be DLT evaluable from the date of first dose and the DLT window for these patients will be 28 days from C1D1.
	DLTs are defined as follows:
	• **Hematologic Toxicities**
	  • Grade 4 neutropenia lasting >7 days
	  • Grade ≥3 febrile neutropenia
	  • Grade 4 thrombocytopenia
	  • Grade ≥3 thrombocytopenia lasting >7 days or associated with clinically significant bleeding
	  • Grade 4 anemia
	• **Non-hematologic Toxicities**
	  • Any dose reduction required during Cycle 1 due to an AE
	  • Any treatment delay of >7 consecutive days during Cycle 1 due to study drug-related Grade ≥2 AEs that fail to resolve to baseline or Grade ≤1
	  • Any case of Hy's law defined as AST or ALT >3 × ULN with concurrent total bilirubin >2 × ULN, absence of cholestasis (elevated alkaline phosphatase (ALP)

	>2 × ULN), and no alternative etiology which can explain the combination of increased AST or ALT and total bilirubin, such as viral hepatitis A through E, other preexisting or acute liver disease, or another drug capable of causing the observed injury • Any Grade ≥3 increase in AST/ALT (only for subjects without hepatic metastasis and with baseline values within normal limits) • AST/ALT >5 × ULN for ≥14 days or any AST/ALT >8 × ULN (only for subjects with hepatic metastasis or with abnormal baseline values) • Grade 3 nausea, vomiting, or diarrhea that does not resolve to Grade ≤2 in ≤72 hours • Any Grade 4 vomiting or diarrhea (life-threatening; urgent medical intervention indicated) irrespective of duration • Any non-clinically significant Grade 3 or higher electrolyte imbalance that does not correct to Grade ≤1 in ≤5 days • Any Grade 3 or Grade 4 clinically significant electrolyte imbalance (life-threatening; urgent medical intervention indicated) irrespective of duration • Unless specifically noted in other DLT criteria any Grade ≥3 (AE or laboratory abnormality) toxicity that does not resolve to Grade ≤2 within 7 days despite maximal medical intervention, except for the following: ▪ Grade 3 neuropathy in subjects with pre-existing Grade 2 neuropathy • Any other Grade ≥3 toxicity (except those noted above) for which either the Principal Investigator or Sponsor deems further dose escalation inappropriate • Carboplatin Cycle 2 Day 1 dose reduction (AUC not total dose) or carboplatin Cycle 2 Day 1 dose interruption for >7 days ▪ An allergic reaction to carboplatin or any AEs associated with the allergic reaction during Cycle 1 will not be considered a DLT. The subject will be noted as inevaluable and will be replaced. Any death not clearly due to underlying disease or an extraneous cause A subject who experiences a DLT may remain in the study and continue receiving study drug(s) at a lower dose if the Investigator deems the potential benefit outweighs the risk and that the subject is not eligible for, and/or interested in, an alternative therapy after consultation and agreement with the Medical Monitor. AEs occurring in treatment Cycle 2 or later will be collected, analyzed, and discussed with the Study Committee to help inform the selection of doses for subsequent study cohorts, including the option of dose reduction. If cumulative toxicities are observed requiring dose reductions in 1 of 3 or more subjects, dose escalation may be halted and more subjects may be treated at that or a lower dose level.
Pharmacokinetic Parameters:	The PK parameters of PLX2853 will be assessed by measuring the AUC from time zero to time of last observed concentration hours postdose ($AUC_{0\text{-last}}$), AUC from time zero extrapolated to 24 hours ($AUC_{0\text{-}24}$), AUC from time zero extrapolated to infinite time ($AUC_{0\text{-}\infty}$), C_{max}, time to C_{max} (T_{max}), terminal elimination half-life ($T_{1/2}$), and accumulation ratio at steady state. Dose proportionality following study dosing will be explored by analyzing natural log-transformed PK variables, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate.

Pharmacodynamic Parameters:	Planned biomarker analyses for PDx include, but are not limited to: • Gene expression, nucleic acid sequencing, histochemical and/or protein analyses of plasma, peripheral blood cells, and/or tumor tissue • Analysis of homologous recombination deficiency (HRD) status Exploratory analysis of biomarker samples may also be performed to learn about the drug and disease properties.
Efficacy Parameters:	Response to treatment will be evaluated using investigator-determined RECIST v1.1 criteria. Disease control rate (DCR) will be calculated as the percentage of subjects with confirmed complete response (CR), PR, or SD. Progression-free survival (PFS) will be calculated for each subject as the number of days from the first day of PLX2853 treatment (Cycle 1 Day 1) to the date of the first documented disease progression or date of death from any cause, whichever occurs first. Duration of response (DOR) will be calculated for each subject with a response as the number of days from the date of first response (PR or CR confirmed at least 28 days later) to the date of the first documented disease progression or date of death from any cause, whichever occurs first. Overall survival (OS) will be calculated for each subject as the number of days from the first day of PLX2853 treatment (Cycle 1 Day 1) to the date of death from any cause.
Safety Parameters:	Safety variables to be assessed will include assessment of AEs, physical examinations (including weight), laboratory test results (hematology, clinical chemistry, coagulation, serum inflammation marker, and urinalysis), ECG, and vital signs.
Endpoints:	**Phase 2a (PLX2853 monotherapy):** Primary endpoint: • Overall response rate (ORR) as measured by RECIST v1.1 **Phase 1b (PLX2853 + carboplatin combination):** Primary endpoint: • Establish the MTD/RP2D for the combination of PLX2853 + carboplatin **Phase 2a (PLX2853 + carboplatin combination):** Primary endpoint: • ORR as measured by RECIST v1.1 **All Phases:** Secondary endpoints: • Incidence of treatment-emergent adverse events, changes in safety parameters, and unacceptable toxicities • DOR • DCR • PFS • OS • PLX2853 PK parameters following single and repeated dosing Exploratory endpoint: • Analysis of peripheral blood and tumors for dose- and exposure-dependent changes in the expression of BET target genes

Statistical Considerations:	**Phase 1b (PLX2853 + carboplatin combination):** The study will employ a standard 3 + 3 design in order to determine the MTD/RP2D taking into consideration safety, PK, and PDx data (if applicable). Data will be tabulated and evaluated by descriptive statistics. Statistical analyses for the primary objectives will be descriptive only, with no hypothesis testing. Summary tables will present results for each dose cohort. Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Response to treatment will be evaluated by investigator-determined response using RECIST v1.1 criteria. **Phase 2a (PLX2853 Monotherapy) and Phase 2a (PLX2853 + carboplatin combination):** The primary objectives of the Phase 2a cohorts of the study are to determine the antitumor activity (ORR) of PLX2853 monotherapy or PLX2853 + carboplatin combination. Response to treatment will be evaluated using investigator-determined RECIST v1.1 criteria, with a minimum interval for confirmation of CR and PR of 4 weeks. Each Phase 2a cohort will enroll up to 26 evaluable subjects using a Simon's 2-stage design in which initially 12 evaluable subjects are enrolled. In the monotherapy cohort, the safety lead in of 6 subjects dosed at the level selected for Phase 2a will be included in the group of 12 evaluable subjects for stage 1. If ≥33% DLTs are seen during the initial safety lead in, the Safety Committee will convene to consider a dose reduction. If a dose reduction is deemed appropriate, the subjects in the initial safety lead in will need to be replaced and a repeat 6 subject safety lead in will need to be conducted at this lower dose. If 2 or more responses are observed in 12 evaluable subjects, another 14 evaluable subjects will be enrolled for a total of 26 subjects to that cohort. If 6 or more responses are observed, the study has 80% power with alpha of 0.05 to reject the ORR of 10% in favor of the ORR of 30%. Recruitment will stop within a cohort if no more than 1 response is observed after the initial 12 evaluable subjects have been accrued. ORR will be summarized per cohort along with their 95% confidence intervals (CIs). A 2-sided 95% CI will be calculated for the true response rate based on the Clopper Pearson method.

SYNOPSIS TABLE 1: PHASE 2A PLX2853 MONOTHERAPY SCHEDULE OF EVENTS

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1					C2	C3+[2]		
	STUDY DAY►	-28 to -1	-4 or -3	1	8	15	22	1	1	30-day FU[3]	LTFU
	WINDOW (days)►				± 2	± 2	± 2	+ 3	± 5	± 7	± 14
Informed Consent		X									
History	Medical history	X									
	Demographics	X									
Vital	Vital signs[4]	X	X[23]	X	X	X	X	X	X	X	
	Height	X									
	Weight	X	X[23]	X	X	X	X	X	X	X	
Safety	Physical exam[5]	X	X[23]	X[6]	X	X	X	X	X	X	
	ECOG	X	X[23]	X[6]	X	X	X	X	X	X	
	12-lead ECG[7]	X	X[23]	X		X		X	X	X	
Lab	PG sample	X									
	Hematology[8]	X[1]	X[23]	X[6]	X	X	X	X	X	X	
	Chemistry[9]	X[1]	X[23]	X[6]	X	X	X	X	X	X	
	Coagulation tests[10]	X[1]	X[23]	X[6]	X	X	X	X	X	X	
	Tumor markers[11]	X[1]	X[23]	X[6]				X	X	X	
	Urinalysis[12]	X[1]	X[23]	X[6]	X	X	X	X	X	X	
	Serum c-reactive protein	X[1]	X[23]	X	X	X	X	X	X	X	
	Pregnancy test	X[1]								X[13]	
	Hepatitis A/B/C & HIV testing[14]	X									
	PK sample[15,16,17]		X[23]	X		X		X	X	X	
	Biomarker (PDx) blood sample[15]		X[23]	X		X		X	X	X	
Medications, Non-drug Treatments, Radiotherapy	Prior treatment	X									
	Concomitant	X									
AE	AE[18]	X									

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1					C2	C3+[2]		
	STUDY DAY►	-28 to -1	-4 or -3	1	8	15	22	1	1	30-day FU[3]	LTFU
	WINDOW (days)►				± 2	± 2	± 2	+ 3	± 5	± 7	± 14
Treatment Response	Archival tissue sample	X									
	Paired biopsy for malignant lesion (mandatory)[19]	X						X			
	Response assessment[20]	X							Every 2 cycles		X[22]
Study Treatment	PLX2853 administration[17]		X[24]	Daily administration for 28 days (full cycle)							
	Low fat meal		X[24]								
	Study drug compliance via diary review and accountability[21]				X	X	X	X	X	X	
Survival	Survival follow-up[22]										X[22]

30-day FU = 30-day follow-up visit; AE = adverse event; C = cycle; CA-125 = cancer antigen 125; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LTFU = long-term follow-up; PDx = pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetic, SCR = screening

1 All Screening laboratory tests should be performed within 10 days of C1D1 unless otherwise specified. Screening serum pregnancy test must be negative within 7 days prior to C1D1 for women of child-bearing potential. A complete list of required tests is found in Appendix 1 to the protocol.

2 If the subject does not have any ongoing Grade 2 or higher treatment-related AEs and following discussion with the Medical Monitor, subjects on treatment longer than 12 cycles may be given the option to only have study visits on cycles with a response assessment (every 2 cycles).

3 The 30-day FU Visit should occur approximately 30 days after the last dose of PLX2853 or prior to starting any new anti-cancer therapy, whichever occurs first.

4 Predose vital signs must be obtained on PK days. On non-PK/non-PDx days, vital signs do not need to be predose and subjects may self-administer PLX2853 at home either prior to or after their clinic visit (if applicable).

5 Complete physical examination at Screening and 30-day FU only. All other physical examinations may be abbreviated and symptom-directed.

6 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation, urinalysis, and tumor markers do not need to be repeated if these assessments from Screening occurred within 3 days of C1D1 unless a change in status is suspected. Subjects must continue to meet all eligibility criteria that are repeated at the time of initiation of C1D1 dosing. Subjects participating in the optional Food Effect sub-study must complete all C1D1 assessments on C1D1, however they are not required to reconfirm eligibility.

7 All ECGs are predose and single tracings on the specified days and only Screening and predose C1D1 should be done in triplicate (approximately 10 seconds per ECG over a 5-minute period). Standard 12-lead ECG with QTcF calculation. Fridericia's correction is required. $QTcF = (QT)/3\sqrt{(RR)}$. For subjects participating in the optional Food Effect sub-study, single tracings ECGs should be obtained on C1D-4 or -3 at predose and 0.5, 1, 2, 3, and 5 hours postdose.

8 Hematology evaluation must include complete blood count with differential and platelet count. A complete list of required tests is found in Appendix 1 to the protocol.

9 Chemistry evaluation must include a complete chemistry panel including liver transaminases and gamma-glutamyl transferase. A complete list of required tests is found in Appendix 1 to the protocol.

10 Coagulation evaluation must include prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen, d-dimer, and Factor VII. A complete list of required tests is found in Appendix 1 to the protocol.

11 To be performed as per institutional practice guidelines. For subjects with ovarian cancer, obtain the 2 most recent CA-125 levels prior to study entry.

12 Urinalysis with urine dipstick is sufficient; if there is significant proteinuria, hematuria, or pyuria, a microscopic examination should be obtained. A complete list of required tests is found in Appendix 1 to the protocol.

13 Serum or urine pregnancy test to be collected at the 30-day FU visit.

14 Serology testing for hepatitis A, B, and C, and HIV should be performed within 28 days of C1D1 if the subject is taking ≤30 µg/day biotin. If the subject is taking >30 µg/day biotin, the subject must lower their daily biotin intake to ≤30 µg and wait 14 days before hepatitis A, B, and C serology testing can be performed (elevated levels of biotin may interfere with viral serology testing).

15

Assessment	**C1D-4 or D-3 (if applicable)**	**C1D1**	**C1D15**	**C2–4 D1**	**C5+ D1**	**30-day FU**
PK	Predose and 0.5, 1, 2, 3, and 5 hours postdose	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose and 1 and 3 hours postdose	Predose	Anytime
PDx	Predose and 3 and 5 hours postdose	Predose and 3 and 5 hours postdose	Predose and 3 hours postdose	Predose	Predose	Anytime

Note: All PK samples should be collected at the specified time points ±10 minutes at the 0.5- and 1-hour sample and ±30 minutes at subsequent time points. PK samples should be collected after the corresponding ECGs have been obtained. Multiple PDx samples and sample types (e.g., serum, whole blood, plasma) may be collected at a given timepoint (detailed sample collection information is provided in the Laboratory Manual).

16 On PK days where a full PK profile is collected (e.g., C1D-3 or C1D-4 (as applicable) C1D1, C1D15), subjects should fast at least 8 hours (10 hours on fed dosing day for the Food Effect sub-study) before dose administration and 1 hour (4 hours on fed dosing days for the Food Effect sub-study) after administration of PLX2853. On other PK sample collection days, subject should fast for 2 hours prior to their visit. During the fasting period, subjects may eat a low-fat snack (e.g., crackers, dry toast, etc.) if they experience gastrointestinal issues following dosing.

Additional samples for PK may be collected if a subject experiences a DLT, serious adverse event, AE of special interest, dose modification, or at the Sponsor's request. The time since the last dose of PLX2853 should be noted. Samples for PK collected for any dose modification should be at predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable) within 2 weeks of the modification or at the next scheduled clinic visit, whichever occurs closest to the new dosing regimen.

17 On non-PK days, subjects should fast at least 2 hours before administration and 1 hour after administration of PLX2853, unless otherwise specified. Subjects should be instructed not to take their PLX2853 dose at home on PK or PDx collection days. If alternate day dosing is used, subjects will be instructed on which days to take PLX2853 (e.g., even or odd numbered days).

18 AE monitoring occurs both predose and postdose on days when PLX2853 is taken in the clinic. All AEs will be monitored for approximately 30 days after the last dose of study drug or prior to starting any new anti-cancer therapy, whichever occurs first.

19 If the archival tissue was collected within 2 months of Screening, a fresh sample does not need to be collected at Screening.

20 Radiographic assessment of tumor burden will occur at least approximately every 2 cycles, or more frequently as clinically indicated. Screening assessment of tumor burden may be within 28 days of scheduled C1D1.

21 Collection of completed dosing diary and distribution of new diary to occur at the beginning of each cycle.

22 Subjects will be followed until death, withdrawal of consent, or loss to follow-up according to the following schedule: every 3 months for the first 2 years after the 30-day follow-up visit and every 6 months thereafter. Survival follow-up can be via clinic visit, phone call to the subject or referring physician, or other method deemed appropriate by the site, and should assess survival, progression, subsequent therapy, and response. Any subject with a confirmed response who discontinues treatment for reasons other than disease progression will continue to be followed per standard of care and no less than every 3 months until documented disease progression, initiation of a new anti-cancer treatment, or 1 year from discontinuation of study treatment. Radiographic scan data will be collected and if scan data are not available, a scan will be obtained every 3 months until 6 months of radiographic follow-up after confirmed response has been obtained.

23 For the optional Food Effect sub-study patients only: Predose assessments for Day -4 or -3 can be completed 1 day prior to fed dosing day. ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation, urinalysis, and tumor markers do not need to be repeated if these assessments from Screening occurred within 3 days of Day -4 or -3 unless a change in status is suspected. Subjects must continue to meet all eligibility criteria that are repeated at the time of initiation of Day -4 or -3 dosing (or 1 day prior as permitted above). All C1D1 assessments are required for these patients, however they are already considered enrolled and will not be required to reconfirm eligibility.

24 Subjects participating in the optional Food Effect sub-study should present to clinic following an overnight fast of at least 10 hours. The subject will consume a low fat meal (see Section 5.2.4 for further details) in 30 minutes or less and complete their dose of PLX2853 within 30 minutes of starting administration with at least 8 ounces of water (and no more than 60 minutes from beginning the meal to completion of PLX2853 dose).

SYNOPSIS TABLE 2: PHASE 1B PLX2853 + CARBOPLATIN DOSE ESCALATION SCHEDULE OF EVENTS

ASSESSMENTS▼	**PROCEDURE▼**	**SCR[1]**	**C1**				**C2**		**C3+[2]**		
	STUDY DAY►	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**30-day FU[3]**	**LTFU**
	WINDOW (days)►			**± 2**	**± 2**	**± 2**	**+ 3**	**± 3**	**± 5**	**± 7**	**± 14**
Informed Consent		X									
History	Medical history	X									
	Demographics	X									
Vital	Vital signs[4]	X	X	X	X	X	X	X	X	X	
	Height	X									
	Weight	X	X	X	X	X	X	X	X	X	
Safety	Physical exam[5]	X	X[6]	X	X	X	X	X	X	X	
	ECOG	X	X[6]	X	X	X	X	X	X	X	
	12-lead ECG[7,15]	X	X		X		X	X	X	X	
Lab	PG sample	X									
	Hematology[8]	X[1]	X[6]	X	X	X	X	X	X	X	
	Chemistry[9]	X[1]	X[6]	X	X	X	X	X	X	X	
	Coagulation tests[10]	X[1]	X[6]	X	X	X	X	X	X	X	
	Tumor markers[11]		X[6]				X		X	X	
	Urinalysis[12]	X[1]	X[6]	X	X	X	X	X	X	X	
	Serum c-reactive protein		X	X	X	X	X		X	X	
	Pregnancy test	X[1]								X[13]	
	Hepatitis A/B/C and HIV testing[14]	X									
	PK sample[15,16,17]		X		X		X		X	X	
	Biomarker (PDx) blood sample[15]		X		X		X		X	X	
Medications, Non-drug Treatments, Radiotherapy	Prior treatment	X									
	Concomitant	X									
AE	AE[18]	X									

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1				C2		C3+[2]		
	STUDY DAY►	**-28 to -1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**30-day FU[3]**	**LTFU**
	WINDOW (days)►			**± 2**	**± 2**	**± 2**	**+ 3**	**± 3**	**± 5**	**± 7**	**± 14**
Treatment Response	Archival tissue sample	X									
	Paired biopsy for malignant lesion (Optional)[19]	X					X				
	Response assessment[20]	X							Every 2 cycles		X[22]
Study Treatment	PLX2853 administration[17]	Daily administration for 28 days (full cycle)									
	Carboplatin administration	Administration at least 2 hours after PLX2853 dosing using a target AUC of 5 mg•min/mL on Day 1 of each 28-day treatment cycle per label									
	Study drug compliance via diary review and accountability[21]			X	X	X	X	X	X	X	
Survival	Survival follow-up[22]										X[22]

30-day FU = 30-day follow-up visit; AE = adverse event; AUC = area under the concentration-time curve; C = cycle; CA-125 = cancer antigen 125; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LTFU = long-term follow-up; PDx = pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetic, SCR = screening

1 All Screening laboratory tests should be performed within 10 days of C1D1 unless otherwise specified. Screening serum pregnancy test must be negative within 7 days prior to C1D1 for women of child-bearing potential. A complete list of required tests is found in Appendix 1 to the protocol.

2 If the subject does not have any ongoing Grade 2 or higher treatment-related AEs and following discussion with the Medical Monitor, subjects on treatment longer than 12 cycles may be given the option to only have study visits on cycles with a response assessment (every 2 cycles).

3 The 30-day FU Visit should occur approximately 30 days after the last dose of PLX2853 or prior to starting any new anti-cancer therapy, whichever occurs first.

4 Predose vital signs must be obtained on PK days. On non-PK/non-PDx days, vital signs do not need to be predose and subjects may self-administer PLX2853 at home either prior to or after their clinic visit (if applicable).

5 Complete physical examination at Screening and 30-day FU only. All other physical examinations may be abbreviated and symptom-directed.

6 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation, and urinalysis do not need to be repeated if these assessments from Screening occurred within 3 days of C1D1 unless a change in status is suspected. Subjects must continue to meet all eligibility criteria that are repeated at the time of initiation of C1D1 dosing.

7 All ECGs are single tracings on the specified days and only Screening and predose C1D1 should be done in triplicate (approximately 10 seconds per ECG over a 5-minute period). Standard 12-lead ECG with QTcF calculation. Fridericia's correction is required. QTcF = (QT)/3√(RR).

8 Hematology evaluation must include complete blood count with differential and platelet count. A complete list of required tests is found in Appendix 1 to the protocol.

9 Chemistry evaluation must include a complete chemistry panel including liver transaminases and gamma-glutamyl transferase. A complete list of required tests is found in Appendix 1 to the protocol.

10 Coagulation evaluation must include prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen, d-dimer, and Factor VII. A complete list of required tests is found in Appendix 1 to the protocol.

11 To be performed as per institutional practice guidelines. For subjects with ovarian cancer, obtain the 2 most recent CA-125 levels prior to study entry.

12 Urinalysis with urine dipstick is sufficient; if there is significant proteinuria, hematuria, or pyuria, a microscopic examination should be obtained. A complete list of required tests is found in Appendix 1 to the protocol.

13 Serum or urine pregnancy test to be collected at the 30-day FU visit.

14 Serology testing for hepatitis A, B, and C, and HIV should be performed within 28 days of C1D1 if the subject is taking ≤30 µg/day biotin. If the subject is taking >30 µg/day biotin, the subject must lower their daily biotin intake to ≤30 µg and wait 14 days before hepatitis A, B, and C serology testing can be performed (elevated levels of biotin may interfere with viral serology testing).

15

Assessment	C1D1	C1D15	C2+D1	C2D15	30-day FU
ECG	Predose and at 0.5, 1, 2, 3, and 5 hours postdose	Predose and at 0.5, 1, 2, 3, and 5 hours postdose	Predose and 1 hour postdose (±30 minutes) at the start of each cycle	Predose and 1 hour postdose (±30 minutes)	Anytime
PK	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose and 1, and 3 hours postdose	N/A	Anytime
PDx	Predose and 3, and 5 hours postdose	Predose and 3 hours postdose	Predose	N/A	Anytime

Note: All postdose ECGs should be collected at the specified time point ±30 minutes unless otherwise stated. Multiple PDx samples and sample types (e.g., serum, whole blood, plasma) may be collected at a given timepoint (detailed sample collection information is provided in the Laboratory Manual).

Note: All PK samples should be collected at the specified time points ±10 minutes at the 0.5- and 1-hour sample and ±30 minutes at subsequent time points. PK samples should be collected after the corresponding ECGs have been obtained.

16 On PK days where a full PK profile is collected (e.g., C1D1, C1D15), subjects should fast at least 8 hours before dose administration and 1 hour after administration of PLX2853. On other PK sample collection days, subject should fast for 2 hours prior to their visit. During the fasting period, subjects may eat a low-fat snack (e.g., crackers, dry toast, etc.) if they experience gastrointestinal issues following dosing.

Additional samples for PK may be collected if a subject experiences a DLT, serious adverse event, AE of special interest, dose modification, or at the Sponsor's request. The time since the last dose of PLX2853 should be noted. Samples for PK collected for any dose modification should be at predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable) within 2 weeks of the modification or at the next scheduled clinic visit, whichever occurs closest to the new dosing regimen.

17 On non-PK days, subjects should fast at least 2 hours before administration and 1 hour after administration of PLX2853, unless otherwise specified. Subjects should be instructed not to take their PLX2853 dose at home on PK or PDx collection days. If alternate day dosing is used, subjects will be instructed on which days to take PLX2853 (e.g., even or odd numbered days).

18 AE monitoring occurs both predose and postdose on days when PLX2853 is taken in the clinic. All AEs will be monitored for approximately 30 days after the last dose of study drug or prior to starting any new anti-cancer therapy, whichever occurs first.

19 If the archival tissue was collected within 2 months of Screening, a fresh sample does not need to be collected at Screening.

20 Radiographic assessment of tumor burden will occur at least approximately every 2 cycles, or more frequently as clinically indicated. Screening assessment of tumor burden may be within 28 days of scheduled C1D1.

21 Collection of completed dosing diary and distribution of new diary to occur at the beginning of each cycle.

22 Subjects will be followed until death, withdrawal of consent, or loss to follow-up according to the following schedule: every 3 months for the first 2 years after the 30-day follow-up visit and every 6 months thereafter. Survival follow-up can be via clinic visit, phone call to the subject or referring physician, or other method deemed appropriate by the site, and should assess survival, progression, subsequent therapy, and response. Any subject with a confirmed response who discontinues treatment for reasons other than disease progression will continue to be followed per standard of care and no less than every 3 months until documented disease progression, initiation of a new anti-cancer treatment, or 1 year from discontinuation of study treatment. Radiographic scan data will be collected and if scan data are not available, a scan will be obtained every 3 months until 6 months of radiographic follow-up after confirmed response has been obtained.

SYNOPSIS TABLE 3: PHASE 2A PLX2853 + CARBOPLATIN DOSE EXPANSION SCHEDULE OF EVENTS

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1				C2	C3+[2]		
	STUDY DAY►	-28 to -1	1	8	15	22	1	1	30-day FU[3]	LTFU
	WINDOW (days)►			± 2	± 2	± 2	+ 3	± 5	± 7	± 14
Informed Consent		X								
History	Medical history	X								
	Demographics	X								
Vital	Vital signs[4]	X	X	X	X	X	X	X	X	
	Height	X								
	Weight	X	X	X	X	X	X	X	X	
Safety	Physical exam[5]	X	X[6]	X	X	X	X	X	X	
	ECOG	X	X[6]	X	X	X	X	X	X	
	12-lead ECG[7]	X	X		X		X	X	X	
Lab	PG sample	X								
	Hematology[8]	X[1]	X[6]	X	X	X	X	X	X	
	Chemistry[9]	X[1]	X[6]	X	X	X	X	X	X	
	Coagulation tests[10]	X[1]	X[6]	X	X	X	X	X	X	
	Tumor markers[11]		X[6]				X	X	X	
	Urinalysis[12]	X[1]	X[6]	X	X	X	X	X	X	
	Serum c-reactive protein		X	X	X	X	X	X	X	
	Pregnancy test	X[1]							X[13]	
	Hepatitis A/B/C and HIV testing[14]	X								
	PK sample[15,16,17]		X		X		X	X	X	
	Biomarker (PDx) blood sample[15]		X		X		X	X	X	
Medications, Non-drug Treatments, Radiotherapy	Prior treatment	X								
	Concomitant	X								
AE	AE[18]	X								

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1				C2	C3+[2]		
	STUDY DAY►	-28 to -1	1	8	15	22	1	1	30-day FU[3]	LTFU
	WINDOW (days)►			± 2	± 2	± 2	+ 3	± 5	± 7	± 14
Treatment Response	Archival tissue sample	X								
	Paired biopsy for malignant lesion (mandatory)[19]	X					X			
	Response assessment[20]	X						Every 2 cycles		X[22]
Study Treatment	PLX2853 administration[17]	Daily administration for 28 days (full cycle)								
	Carboplatin administration	Administration at least 2 hours after PLX2853 dosing using a target AUC of 5 mg•min/mL on Day 1 of each 28-day treatment cycle per label								
	Study drug compliance via diary review and accountability[21]			X	X	X	X	X	X	
Survival	Survival follow-up[22]									X[22]

30-day FU = 30-day follow-up visit; AE = adverse event; AUC = area under the concentration-time curve; C = cycle; CA-125 = cancer antigen 125; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LTFU = long-term follow-up; PDx = pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetic; SCR = screening

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15

Assessment	C1D1	C1D15	C2–4 D1	C5+ D1	30-day FU
PK	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose and 1 and 3 hours postdose	Predose	Anytime
PDx	Predose and 3 and 5 hour postdose	Predose and 3 hours postdose	Predose	Predose	Anytime

Note: All PK samples should be collected at the specified time points ±10 minutes at the 0.5- and 1-hour sample and ±30 minutes at subsequent time points. PK samples should be collected after the corresponding ECGs have been obtained. Multiple PDx samples and sample types (e.g., serum, whole blood, plasma) may be collected at a given timepoint (detailed sample collection information is provided in the Laboratory Manual).

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1.0 BACKGROUND AND STUDY RATIONALE

1.1 Background

Cancers are biologically heterogeneous diseases that are characterized by a medley of genomic aberrations and mutations. Recently, aberrant regulation of epigenetic processes has emerged as a common feature underlying many malignancies, with epigenetic regulation of gene expression impacting both the initiation and maintenance of these malignancies. Bromodomain and extra terminal domain (BET) proteins in particular serve as a common driver of malignancy through their effects on the expression of a specific set of genes essential for tumor growth and survival.

PLX2853 is an orally active, small molecule inhibitor of BET bromodomain-mediated interactions. PLX2853 exhibits low nanomolar potency in blocking all 4 BET family members (BRD2, BRD3, BRD4, and BRDT).

1.2 Evidence of a Role for BET Proteins in Solid Tumors

Bromodomains are protein interaction modules that recognize acetylated lysine residues on target proteins. Bromodomains are present in diverse nuclear proteins and function as epigenetic readers for transcriptional regulators and chromatin modifying enzymes (Filippakopoulos 2012). Dysfunction of a subset of bromodomain-containing proteins has been strongly associated with the development of cancer (Muller 2011). In particular, the BET family bromodomain proteins (BRD2, BRD3, BRD4, BRDT) have recently received much attention with the development of potent, cell-active inhibitors (Filippakopoulos 2012; Dawson 2011). Pharmacological inhibition of BET proteins leads to selective killing of tumor cells across a broad range of malignancies (Filippakopoulos 2012; Picaud 2013; Delmore 2011; Zuber 2011; Lockwood 2012; Cheng 2013).

BET proteins facilitate the development of many types of human neoplasms by serving as the epigenetic regulators of many genes essential for tumor growth and survival. BET proteins are expressed as malignant oncogenic fusions in several rare forms of cancer. In particular, through chromosomal translation, BRD4 forms in-frame fusions with the NUT gene to initiate an aggressive cancer called NUT midline carcinoma (French 2003). The resulting BRD4NUT oncoprotein is an aberrant transcriptional regulator that relies on the bromodomains of BRD4 for its oncogenic function (Alekseyenko 2015). Studies using patient-derived NUT midline carcinoma xenografts provided the first demonstration of efficacy for a BET inhibitor in a preclinical cancer model (Filippakopoulos 2010). BET inhibitors have since shown therapeutic effects in other solid tumors (Filippakopoulos 2010; Nicodeme 2010). For non-small cell lung cancer, the effects correlate with suppression of FOSL1 expression (Lockwood 2012; Shimamura 2013), while the sensitivity of small cell lung cancer appears to be mediated by regulation of ASCL1 gene expression (Lenhart 2015). Neuroblastomas that harbor MYCN amplifications are also sensitive to BET inhibition, correlating with suppression of MYCN transcription (Puissant 2013; Wyce 2013). In addition, BET inhibitors have also shown antitumor activity in genetically diverse glioblastomas (Cheng 2013; Pastori 2015), MYC-amplified

medulloblastoma (Bandopadhayay 2014; Henssen 2013), castration-resistant prostate cancer (Asangani 2014; Cho 2014), basal-like and Her2-positive breast cancer (Shi 2014; Stuhlmiller 2015), and melanoma (Ambrosini 2011; Heinemann 2015).

1.3 Role of BET Inhibitors in Platinum-resistant Epithelial Ovarian Cancer

Ovarian cancer, specifically epithelial ovarian cancer (EOC) (nearly 90% of all cases), is the leading cause of death from gynecologic malignancies in the United States. In 2018, it was estimated that 22,240 new diagnoses and 14,070 deaths had occurred. The incidence of ovarian cancer increases with age, and the median age at diagnosis is 63 years. Unfortunately, most cases (nearly 70%) present at an advanced stage (NCCN 2020). Ovarian cancer is a diverse and genomically complex disease. EOC has been classified into 5 histotypes including high-grade serous, low-grade serous, clear cell, endometrioid, and mucinous.

The primary treatment of advanced ovarian cancer consists of surgical debulking plus systemic chemotherapy (usually a combination of a platinum agent and a taxane) in most patients. Some patients are refractory to initial therapy, defined as patients who progress after 2 consecutive chemotherapy regimens without ever achieving a response. Eventually, even patients who respond will relapse. Platinum resistance is defined as progression less than 6 months after the last platinum based therapy. Patients who relapse after 6 months are considered to have platinum-sensitive disease (NCCN 2020).

Multiple single-agent and combination therapy strategies have been utilized in the second-line (or later) setting with the goal to prolong survival and optimize quality of life. For patients with platinum-resistant disease, a number of chemotherapeutic agents are used such as taxanes, liposomal doxorubicin, topotecan, and others, and they appear to have similar response rates. The addition of anti-angiogenic agents such as bevacizumab (delivered as a maintenance strategy) has been shown to improve survival. Several poly-(ADP-ribose) polymerase (PARP) inhibitors may also be used in patients whose tumors harbor BRCA1 or BRCA2 mutations (NCCN 2020; Coward 2015). Despite these advances, the mortality rate for ovarian cancer remains high. Less than 40% of all patients with ovarian cancer are cured. Novel therapies are urgently needed to improve patient outcome.

This study evaluates whether BET inhibitor PLX2853 in combination with platinum represents an effective approach for overcoming platinum resistance. This is based on a number of preclinical studies that identified BET proteins as potential therapeutic targets in ovarian cancer (Baratta 2015; Zhang 2016; Karakashev 2017; Wilson 2018; Rhyasen 2018). Suppression of BRD4 using small-molecule BET inhibitors led to robust and broad antitumor effects across all subclasses of ovarian cancer (Zhang 2016). In particular, BRD4 is frequently amplified in high-grade serous ovarian cancer (HGSOC), the most common and malignant form of EOC (Baratta 2015; Ucar 2015). BRD4 amplification is oncogenic; in treatment-naive HGSOC, BRD4 amplification correlates with poor clinical outcomes (Ucar 2015). Neuregulin-1 (NRG1) functions as a critical effector in BRD4-mediated cellular transformation. BRD4 regulation of NRG1 expression is mediated by the switch/sucrose non-fermentable (SWI/SNF) nucleosome

remodeling complex. BRD4 amplification confers sensitivity to BET inhibition in HGSOC and NRG1 suppression represents a specific pharmacodynamics (PDx) marker. The pan-subtype cell-cycle arrest by BET inhibition, however, is potentially mediated by down regulation of FOXM1 proto-oncogene, a key driver of EOC.

A more direct link between BET and platinum-resistant tumors concerns DNA repair (Karakashev 2017; Yang 2017; Wilson 2018). DNA repair mechanisms, which are fundamental for recognition and removal of platinum adducts, are closely associated with the development of drug resistance. Selection for platinum-resistance, thus, enriches tumors with functional DNA repairs. This also represents the patient population where none of the current treatments, including PARP inhibitors, are effective. In HGSOC, there is a significant enrichment of DNA damage repair and cell-cycle checkpoint-regulating genes (e.g., WEE1 and TOPBP1) among BRD4 target genes. Combined BET and PARP inhibition increases DNA damage and cell-cycle checkpoint defects, leading to mitotic catastrophe.

1.4 Role of BET Inhibitors in Advanced Gynecological Malignancies with a Known ARID1A Mutation

Disordered chromatin regulation has emerged as a distinct mechanism contributing to tumor development. In particular, genes encoding subunits of ATP-dependent chromatin remodelers, especially subunits of the SWI/SNF complex, are frequently mutated in a broad array of cancer types (Wilson 2011; Kadoch 2015). Mutually exclusive subunits in the SWI/SNF complex include the DNA targeting members ARID1A and ARID1B as well as the ATPases SMARCA2 and SMARCA4. ARID1A inactivating mutations are the most common alterations of the SWI/SNF complex in gynecological malignancies (Wu 2013; Bitler 2015). In particular, nearly 50% of ovarian clear cell carcinomas (OCCCs) harbor an inactivating mutation in the ARID1A gene (Mabuchi 2016). Loss of ARID1A activates major signaling pathways such as increased PI3K-AKT-MTOR pathway (Caumanns 2018), that confer an advantage to the tumor cells through enhanced proliferation and/or survival. OCCC is a less common form of EOC, comprising <10% of all ovarian cancers with a heterogeneous genomic landscape (Murakami 2017). It is known to be less sensitive to platinum-based chemotherapy (Tan 2013). Once patients progress after platinum-based chemotherapy, there are limited options for them.

Recently, it was shown that loss of ARID1A sensitizes most OCCC to BET inhibition (Berns 2018). In a large panel of OCCC cell lines representing the full spectrum of ARID1A mutation status, knockdown of BET family member BRD2 resulted in enhanced toxicity predominantly in ARID1A mutant cell lines. Small molecule inhibitors of BET (e.g., JQ1 and iBET-762) specifically inhibit proliferation of ARID1A mutated OCCCs, both in vitro and in ovarian clear cell cancer xenografts and patient-derived xenograft models. BET inhibitors cause a reduction in the expression of multiple SWI/SNF members including ARID1B that are synthetic lethal targets in ARID1A mutant cells (Berns 2018; Helming 2014; Kelso 2017). However, ARID1A mutant cell lines with PIK3CA pathway gene mutations did not show a reduction in c-Myc and had a higher half-maximal inhibitory concentration (IC_{50}) for BETi when compared to the ARID1A mutant cell lines that did not have PIK3 pathway mutations

(Berns 2018). Chromatin immunoprecipitation experiments demonstrated specific BRD2 binding to various SWI/SNF member promoter regions.

Information on ARID1A continues to emerge from comprehensive genome-wide analyses with next‑generation sequencers. ARID1A mutations have been found in various types of cancer and occur at high frequency at the early stage of canceration from endometriosis to endometriosis-associated carcinoma in ovarian cancer and also from atypical endometrial hyperplasia to endometrioid adenocarcinoma in endometrial cancer. BET inhibitors such as PLX2853 may have broad utilities as a novel therapy for gynecological cancers expressing loss of function ARID1A mutations.

1.5 PLX2853

Unlike the first generation BET inhibitors including JQ1 (Filippakopoulos 2010), I-BET762 (Mirguet 2013), and OTX015 (Boi 2015), PLX2853 is structurally unrelated to the benzodiazepines. The nonclinical pharmacology, PK, and toxicology profiles of PLX2853 have been characterized in an extensive program of in vitro and in vivo studies. The data from these studies supported clinical development of PLX2853 as a novel epigenetic therapy for certain cancers. PLX2853 is currently in clinical development for both hematopoietic malignancies (Study PLX124-02 [NCT03787498]) and solid tumors (Study PLX124-01 [NCT03297424]). The data to date have demonstrated evidence of antitumor activity with manageable toxicity. In particular, clinical experience with PLX2853 monotherapy in subjects with heavily pretreated ovarian, fallopian, and peritoneal cancers has shown some signs of activity. So far, the dose escalation phase of PLX124-01 has enrolled 7 subjects with ovarian cancers, 2 subjects with endometrial cancers, 1 subject with primary peritoneal cancer, and 1 subject with cervical cancer. Four of these 11 subjects showed initial decreases in the sum of their target lesions after starting PLX2853 monotherapy. The subject with peritoneal cancer achieved a 30% reduction in the sum of their target lesions and remained on therapy for longer than 9 months. These minor responses over a range of doses and in a broad patient segment are encouraging, but suggest that PLX2853 needs to be explored in combination with other agents or in a genomically defined and sensitive population.

1.5.1 Nonclinical Pharmacology

The 4 BET family proteins, BRD2, BRD3, BRD4 and BRDT, share the feature of containing 2 conserved N-terminal bromodomains (BD1 and BD2), an extra terminal domain, and a divergent C-terminal recruitment domain. The dissociation constant (K_d) values of PLX2853 were determined for the 8 isolated BET bromodomains. Based on the measured K_d values, PLX2853 is more potent against isolated bromodomains from the BET proteins BRD2, BRD3, and BRD4 than those from the testes-specific BRDT (Table 1). Within these isolated domains there is a slight preference for binding to the BD2. Structural analyses of the interactions of BET proteins with histone tails suggested that both BD1 and BD2 are involved in the recognition of acetyl-lysine epitopes. Thus, potent inhibition of both bromodomains likely contributes to the overall pharmacological effects of PLX2853. In biochemical assays that examined the binding of

acetylated histone tail to BET proteins containing both bromodomains, PLX2853 displayed potent inhibitory activity (IC_{50} = 4.3 nM for BRD4 and 7.3 nM for BRD2).

Table 1: K_d Values of PLX2853 for Binding to the 8 Bromodomains from 4 BET Proteins

Bromodomain[a]	PLX2853 K_d (nM)
BRD2 (BD1)	0.32
BRD2 (BD2)	0.21
BRD3 (BD1)	0.34
BRD3 (BD2)	0.21
BRD4 (BD1)	0.51
BRD4 (BD2)	0.24
BRDT (BD1)	1.5
BRDT (BD2)	3.9

Source: EXP-15-AD5580

[a] Each assay used a truncated protein containing a single bromodomain. The 2 bromodomains of each BET protein are labeled as BD1 and BD2, respectively.

Binding interactions of PLX2853 to the other 24 isolated bromodomains from 22 different proteins were measured using BROMOscan (EXP-15-AD5580). At a 1 µM concentration, PLX2853 shows interactions with the bromodomains in 3 non-BET proteins, CREBBP, EP300, and TAF1-BD2. The K_d values of PLX2853 were determined for all bromodomains that showed >50% binding in the single concentration primary screen. Of the non-BET proteins, only CREBBP and EP300 had sub-micromolar potencies with K_d values in the 100 nM range.

A functional MYC reporter assay was generated by placing a firefly luciferase gene construct under the control of a minimal cytomegalovirus promoter and tandem repeats of a MYC binding element (E-box) to determine the cellular PDx effect of PLX2853. PLX2853 potently inhibits MYC reporter activity in MV4-11 cells with an IC_{50} of 7.2 nM.

The antitumor effects of PLX2853 were also evaluated in a panel of 14 ovarian cancer cell lines (Table 2). Ovarian cell lines with $ARID1A^{mut}$ cell lines are particularly sensitive to PLX2853. This finding provides a rationale for testing PLX2853 as a potential new therapy in the treatment of OCCC. OCCC is a distinct histopathologic subtype of ovarian cancer and has a high ARID1A mutation frequency (>50%). ARID1A mutations also occur with relatively high frequency in other cancers, supporting broader utility of PLX2853 across a broad spectrum of cancers, especially clear cell cancers arising from ectopic or eutopic endometrium.

Table 2: Antitumor Effects of PLX2853 in Ovarian Cancer Cell Lines

Cell Line	Type	Genotype	IC_{50} (µM)	CI_{95} (µM)[a]
SW626	Ovarian	$ARID1A^{wt}$	0.07	0.034–0.15
OVISE (OCCC)	Ovarian	$ARID1A^{mut}$	0.26	0.14–0.48
SKOV3	Ovarian	$ARID1A^{mut}$	0.49	0.37–0.66
OVTOKO (OCCC)	Ovarian	$ARID1A^{mut}$	0.61	0.33–1.14
ES-2 (OCCC)	Ovarian	$ARID1A^{mut}$, MYC^{AMP}	1.26	0.68–2.36
TOV-112D	Ovarian	$ARID1A^{wt}$	1.31	0.67–2.57
COV 644	Ovarian	NA	1.46	0.70–3.05
OVCAR-8	Ovarian	$ARID1A^{wt}$	1.60	0.85–3.02
A2780	Ovarian	$ARID1A^{mut}$	2.41	1.65–3.53
COV 504	Ovarian	NA	2.42	1.02–5.73
TOV 21G (OCCC)	Ovarian	$ARID1A^{mut}$	3.13	1.74–5.63
OVSAH0	Ovarian	$ARID1A^{wt}$	>20	N/A (>20)
OVCAR-4	Ovarian	$ARID1A^{wt}$	>20	N/A (>20)
PA-1	Ovarian	$ARID1A^{wt}$	>20	N/A (>20)

Source: EXP-15-AD8492

CI_{95} = 95% confidence interval; IC_{50} = half-maximal inhibitory concentration; N/A = not available

[a] 95% confidence interval; individual IC_{50} values when the number of repeats <3.

In vitro data also support the combination of BET inhibitors and topoisomerase I/II inhibitors as an effective approach to treating ovarian cancer. For example, the combination of PLX2853 with irinotecan conferred a synergistic anti-proliferative effect in TOV21G (ovarian) cells. The same effect was observed in small cell lung cancer cells.

The in vivo antitumor activity of PLX2853 was demonstrated in several tumor xenograft models. In particular, Study EXP-17-AF3510 examined the effect of PLX2853 with continuous daily dosing, as well as 5-days on, 2-days off intermittent dosing (QD-5/2) in the ovarian TOV21G xenograft model. Both treatment groups showed significant responses compared to the vehicle control group with minimal body weight loss. PLX2853 dosed at 10 mg/kg continuous daily dosing resulted in 77% tumor growth inhibition (TGI) by the end of study with a steady state area under the concentration-time curve from time zero to 24 hours postdose (AUC_{0-24}) of 8,710 ng•hr/mL. PLX2853 dosed at 20 mg/kg QD-5/2 performed slightly better (85% TGI).

Recently, immunotherapies and especially checkpoint inhibitors have shown significant clinical benefit in selected patient populations. These therapies can offer broader clinical benefit with auxiliary strategies to mitigate the immunosuppressive nature of the tumor microenvironment. A selective BET inhibitor holds promise to improve the efficacy of cancer immunotherapies. By inhibiting the accumulation of immunosuppressive macrophages and myeloid-derived suppressor cells, BET inhibitors have been shown to reprogram the tumor microenvironment to facilitate T cell-mediated antitumor immunity (Zhu 2016). Study EXP-16-AF3502 evaluated the potential of combining PLX2853 with αCTLA4 in the treatment of colorectal cancer using the MC38 syngeneic xenograft model. As single agent, PLX2853 at 6 mg/kg once daily (QD) and αCTLA4

performed equally well, resulting in 78% and 74% TGI, respectively, by the end of a 21-day dosing period. The combined treatment generated stronger efficacy, achieving nearly complete (93%) TGI. A similar TGI (95%) and a higher rate of complete response (CR) were observed when a higher dose of PLX2853 administered every other day was combined with αCTLA4. The 5 animals in this group that had achieved sustained CRs rejected the re-implantation of MC38 tumor cells, illustrating the development of full immunity in these animals (Zhu 2016).

1.5.2 Nonclinical Pharmacokinetics

PLX2853 is an achiral molecule with a molecular weight of 515.6 Da. The absorption, distribution, metabolism, and elimination properties of PLX2853 have been characterized through a comprehensive panel of nonclinical in vitro and in vivo studies. PLX2853 is lipophilic with a logP of 4.15 and a logD (pH 7.4) of 0.93. Because the molecule contains ionizable groups, the aqueous solubility of PLX2853 is pH dependent. PLX2853 is more soluble at both low and alkaline pH. The presence of bio-relevant media (e.g., simulated intestinal or gastric fluid) appears to have minor impact on its aqueous solubility. PLX2853 has a solubility of 94.3 µM (48.6 µg/mL) at pH 7 and is stable in simulated intestinal and gastric fluids. PLX2853 shows high bidirectional permeability across Caco-2 monolayers with a low efflux ratio. Because of its moderate solubility and high permeability, PLX2853 is a Biopharmaceutics Classification System class II drug with oral absorption limited by the dissolution rate.

The preclinical PK of PLX2853 was evaluated in 3 species (mouse, rat, and dog) following intravenous (IV) and oral administration of the compound. PLX2853 exhibited low IV clearance (CL) in all 3 species (CL = 1.68, 2.71, and 2.69 mL/min/kg in mice, rats, and dogs, respectively) with a $T_{1/2}$ of 2 hours or less. Rat and dog, the 2 species selected for preclinical safety testing, were used more extensively to evaluate the PK and bioavailability of oral doses of PLX2853. Because of the limited solubility, an immediate-release amorphous formulation using spray-dried dispersion technology was developed to enhance bioavailability of PLX2853. In both single-dose and repeat-dose PK studies, the T_{max} was usually within 2 hours following oral administration. In the definitive 28-day Good Laboratory Practice (GLP) rat and dog toxicology studies, PLX2853 showed near dose-proportional increase in exposure over the dose range evaluated. Because of the relatively short $T_{1/2}$, only modest level of accumulation was observed at steady state. At top dose, the exposure, in terms of AUC_{0-24}, was slightly lower in females than in males, though differences were less than 2-fold.

In the IND-enabling toxicology studies, PLX2853 was quantified in plasma using fully-validated high performance liquid chromatography (HPLC) tandem mass spectrometry (LC/MS/MS) bioanalytical methods. Two GLP-compliant validated LC/MS/MS chromatographic methods in positive ion mode (ESI+) were used for quantification of PLX2853 in rat and dog plasma samples. A separate method was performed with HPLC coupled with ultraviolet (UV) absorption for dosing solution analysis.

Protein binding of PLX2853 is moderate to high in human (96.1%), monkey (93.4%), dog (95.5%), rat (97.9%), and mouse (95.4%) plasma. PLX2853 is stable in the plasma of all

5 species. In a single-dose tissue distribution study in rats, the brain penetration of PLX2853 was minimal with a brain to plasma ratio of <0.01 two hours after administration of 10 mg/kg oral dose of PLX2853.

PLX2853 is metabolically stable. The metabolic turnover was low for PLX2853 in mouse, rat, dog, monkey, and human S9 fractions (S9-based intrinsic clearance <4.9 µL/min/mg in all 5 species). Liver S9 metabolite profiling identified an oxidation metabolite (labeled M1) in human and dog and no major metabolites in rat. Cytochrome P450 (CYP) reaction phenotyping indicates that CYP2C8 and CYP3A4 are the major contributors for the formation of the PLX2853 oxidative metabolite M1. Their relative contributions to the formation of M1 were similar. However, because the rate of metabolism is so low, CYP2C8 and CYP3A4 inhibitors are not expected to have a significant effect on the clearance of PLX2853.

The excretion profiles of PLX2853 in bile duct-cannulated (BDC) male Sprague Dawley rats following IV administration were determined. Following IV administration of 1, 10, and 25 mg/kg PLX2853 to BDC rats, by 24 hours postdose, 4.08%, 5.56%, and 4.56% and 0.118%, 0.082%, and 0.587% of the administered dose were recovered as PLX2853 in bile and urine, respectively. Based on these data, biliary and urinary excretion of untransformed PLX2853 do not appear to be major routes of elimination of PLX2853 in rats.

The drug-drug interaction potential of PLX2853 was further evaluated by measurement of CYP inhibition using recombinant enzymes and CYP induction potential in human hepatocytes. Studies have also been conducted to assess the potential of PLX2853 as an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), organic anion transporter (OAT)1, OAT3, OCT2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 mediated transport in polarized monolayer of Madin-Darby canine kidney II cells. PLX2853 demonstrated no potential to cause direct or time-dependent inhibition CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. PLX2853 did not induce any of the respective isoforms of CYP1A, CYP2B, and CYP3A genes at all the concentrations tested in human, monkey, dog, and rat hepatocytes except CYP3A in monkey (34% to 49% of the positive control). Compared to vehicle control, PLX2853 at 10 µM inhibited OCT2, OATP1B1, OATP1B3, BCRP, and P-gp mediated transport by 24.4%, 82.4%, 50.7%, 37.2%, and 48.8%, respectively. Considering the plasma protein binding of PLX2853 (96.1% in human), the plasma concentration to achieve 10 µM free fraction is >250 µM, well beyond the anticipated in vivo exposures. Collectively, these results suggest that the risk of in vivo drug-drug interactions is low for PLX2853.

The food effect on the PK of PLX2853 was evaluated following a single oral dose to male beagle dogs under fasted or fed (high fat diet) conditions. This was a single-dose, 2-period cross-over study where each group received a 40 mg oral dose of PLX2853 (two 20 mg strength tablets) while either fasted or fed and then received the alternate treatment (fasted or fed) following a washout period of 4 days (96 hours) between doses.

Dogs receiving the high fat diet had a significant reduction in exposure of PLX2853. The mean peak concentration (C_{max}) values were 903 and 4870 ng/mL for fed and fasted groups,

respectively. The mean AUC_{0-24} values were 3280 and 14,100 ng•hr/mL for fed vs fasted groups, respectively. The geometric mean ratios (fed/fasted) with the calculated 90% confidence intervals (CI_{90}) for the ratios for C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were 17.72% (11.71% to 26.81%), and 25.15% (18.34% to 34.548%), and 25.82% (18.92% to 35.24%), respectively.

1.5.3 Toxicology Studies of PLX2853

The PLX2853 toxicology program is consistent with the guidance provided in the International Council for Harmonisation (ICH) S9 guideline and is comprised of repeat-dose exploratory toxicology studies and definitive 4-week toxicology studies conducted in 2 mammalian species (rat and dog) using the clinically-relevant route of administration (oral) and dosing schedule (continuous daily administration). Additionally, definitive in vitro genotoxicity studies were conducted. Clinically-relevant polymer-based blend formulations of PLX2853 were used in the dose-range finding and definitive in vivo studies. Doses/concentrations of test article used in the definitive studies were corrected for polymer loading and reflect the dose/concentration of active moiety. PLX2853 was administered to rats via oral gavage and to dog via oral capsule. An overview of the PLX2853 toxicology program is provided in Table 3.

Table 3: Overview of PLX2853 Toxicology Program

Study Type (Study Number)	Species and Strain	Method of Administration	Doses (mg/kg/day)[a]
Repeat-dose Toxicity			
14-day dose range-finding (EXP-15-AC2093)	Rat/Crl:CD (Sprague-Dawley)	Oral (gavage)	0, 1[b], 5, 10
28-day definitive (EXP-16-AF1301)	Rat/Crl:CD (Sprague-Dawley)	Oral (gavage)	0, 0.5, 1.5, 5[c]
14-day dose range-finding (EXP-16-AC2095)	Dog/Beagle	Oral (capsule)	0, 1, 3, 6
28-day definitive (EXP-16-AF1302)	Dog/Beagle	Oral (capsule)	0, 0.3, 1[c], 3
Genotoxicity			
Bacterial reverse mutation assay	*S. typhimurium*, *E. coli*	In vitro	≤5000 µg/plate
Chromosome aberration assay	Human (peripheral blood lymphocytes)	In vitro	3 hours without metabolic activation: 3.13–250 µg/mL 3 hours with metabolic activation: 0.783–3.13 µg/mL 22 hours without metabolic activation: 0.0061–0.0244 µg/mL
Other Toxicity Studies			
Phototoxicity assay	NIH/3T3 (ATCC® CRL-1658™)	In vitro	≤50 µM
Hepatocyte cytotoxicity assay	Human	In vitro	0.07–50.00 µM
Cell viability assay	Human kidney (293T) and liver (HepG2) cell lines	In vitro	≤50 µM

HNSTD = highest non-severely toxic dose; NOAEL = no-observed-adverse-effect-level

[a] Unless otherwise specified. For repeat-dose toxicity, the NOAEL is underlined.

[b] NOAEL for females; the NOAEL for males could not be defined.

[c] HNSTD for both males and females. A NOAEL could not be determined for either sex.

The rat and dog were selected for the PLX2853 toxicology program as the rodent and nonrodent toxicology species, respectively, on the basis of in vitro metabolism studies which indicated that metabolism of PLX2853 in rat and dog hepatocytes is qualitatively comparable to that in human hepatocytes.

In both rats and dogs, 14-day exploratory studies were conducted as dose range-finders for subsequent 28-day definitive studies. In rats, QD oral administration of PLX2853 at dose levels of 1, 5, and 10 mg/kg/day for up to 14 consecutive days resulted in moribundity at 10 mg/kg/day in both sexes, resulting in early termination of 10 mg/kg/day animals on Day 7. Adverse test article-related microscopic findings noted in PLX2853-treated rats included: increased minimal to moderate thickness of the femoral physis in males at all dose levels; atrophy and lymphoid depletion in the thymus and lymphoid depletion in the spleen in both sexes at 5 mg/kg/day; and

minimal atretic follicles in the ovary, and an alteration in estrous cyclicity in females at 5 and 10 mg/kg/day. Under the conditions of this study, the highest non-severely toxic dose (HNSTD) of PLX2853 was considered to be 5 mg/kg/day for both sexes. Systemic exposure (AUC_{0-24} and C_{max}) at the HNSTD on Day 13 was 9420 ng•hr/mL and 1580 ng/mL, respectively for males and 2350 ng•hr/mL and 771 ng/mL, respectively, for females. The no-observed-adverse-effect level (NOAEL) for PLX2853 in this study was considered to be 1 mg/kg/day for females but could not be defined for males. Based on the results of this dose range-finding study, PLX2853 dose levels of 0.5, 1.5, and 5 mg/kg/day were selected for evaluation in the subsequent 28-day definitive toxicity study. In the 28-day study, QD oral administration of PLX2853 for a minimum of 28 consecutive days resulted in adverse test article-related effects including reduced body weight gain and food consumption in males at 1.5 and 5 mg/kg/day. Adverse microscopic findings in lymphoid and hematopoietic tissues at the terminal necropsy included: hypocellularity of the bone marrow at 0.5 (females only), 1.5, and 5 mg/kg/day in both sexes, with clinical pathology correlates of decreased mean total white blood cell, absolute lymphocyte, and basophil counts at all dose levels, decreased mean absolute eosinophil counts (males only) at 5 mg/kg/day, and possibly decreased mean platelet count (males only) at 5 mg/kg/day; atrophy of the thymus in males at all dose levels and atrophy and lymphoid necrosis of the thymus in females at 5 mg/kg/day; and lymphoid depletion of the spleen, mesenteric lymph node (males only), and/or thymus in males at all dose levels and in females at 1.5 and 5 mg/kg/day (correlating in males with decreased mean absolute lymphocyte counts, decreased mean thymus and spleen weights at all dose levels, and macroscopic small thymus at 5 mg/kg/day and in females with decreased mean thymus and spleen weights at 1.5 and 5 mg/kg/day). All adverse effects were resolved following the 28-day treatment-free recovery period. Under the conditions of this study, the HNSTD for PLX2853 was considered to be 5 mg/kg/day. Systemic exposure (AUC_{0-24} and C_{max}) at the HNSTD on Day 27 was 1800 ng•hr/mL and 1400 ng/mL, respectively, for males and 1190 ng•hr/mL and 1370 ng/mL, respectively, for females. A NOAEL could not be determined for either sex in this study.

In dogs, QD oral administration of PLX2853 at dose levels of 1, 3, and 6 mg/kg/day for up to 14 consecutive days resulted in overt toxicity in both sexes at the 6 mg/kg/day high-dose level. Two of 3 high-dose male animals were euthanized in moribund condition on Days 5 and 12. As a result, the surviving high-dose animals were scheduled for early termination on Day 13. Adverse test article-related findings in PLX2853-treated dogs included: intestinal mucosal changes, lymphoid depletion, necrosis of lymphoid organs, bone marrow hypocellularity and prolongations of activated partial thromboplastin time (aPTT) in both sexes; atrophy of the thymus, correlating with macroscopic findings and effects on thymic weight in both sexes at 3 mg/kg/day; and lesions in the male reproductive tract at 3 mg/kg/day. Under the conditions of this study, the HNSTD for PLX2853 was considered to be 3 mg/kg/day for both sexes, while the NOAEL was considered to be 1 mg/kg/day for both sexes. Systemic exposure (AUC_{0-24} and C_{max}) at the HNSTD on Day 13 was 5050 ng•hr/mL and 1900 ng/mL, respectively, for males and 879 ng•hr/mL and 203 ng/mL, respectively, for females. Systemic exposure (AUC_{0-24} and C_{max}) at the NOAEL on Day 13 was 2600 ng•hr/mL and 503 ng/mL, respectively, for males and 1230 ng•hr/mL and 333 ng/mL, respectively, for females. Based on the results of this dose

range-finding study, PLX2853 dose levels of 0.3, 1, and 3 mg/kg/day were selected for evaluation in the subsequent 28-day definitive toxicity study. In the 28-day study, all animals administered 0.3 or 1 mg/kg/day PLX2853 survived until scheduled termination, whereas animals administered 3 mg/kg/day PLX2853 were submitted for early termination on the day of the scheduled terminal necropsy. Once daily administration of 3 mg/kg/day PLX2853 resulted in adverse clinical observations indicating severe toxicity, body weight loss, reduced food consumption, altered organ weights, altered hematology, coagulation, and clinical chemistry parameters, and macroscopic and microscopic findings in both males and females. Test article-related effects included: erosion/ulcer and/or hemorrhage in the gastrointestinal tract tissues and lung hemorrhage and inflammation, together with concurrent altered serum electrolytes, prolonged prothrombin time, and aPTT, and decreased platelet and reticulocyte counts at 3 mg/kg/day; tubular degeneration in the testes with associated epididymides and prostate changes at 1 and 3 mg/kg/day; hypocellular marrow in both sexes at all dose levels; and thymic atrophy, lymphoid depletion of Peyer's patches and axillary lymph nodes in both sexes at 3 mg/kg/day. In addition, 1 male in the 0.3 mg/kg/day low-dose group was noted for hemorrhage and inflammation in the lung, which was considered adverse. Following 28 days of treatment-free recovery, microscopic findings had either completely resolved or were considered to be in the process of resolving. Under the conditions of this study, the HNSTD for PLX2853 was considered to be 1.0 mg/kg/day in both sexes. Systemic exposure ($AUC_{0\text{-}24}$ and C_{max}) at the HNSTD on Day 27 was 1940 ng•hr/mL and 935 ng/mL, respectively, for males and 1610 ng•hr/mL and 775 ng/mL, respectively, for females. A NOAEL could not be determined for either sex in this study.

PLX2853 was found to be non-mutagenic in a definitive bacterial reverse mutation assay. In a definitive in vitro chromosome aberration assay conducted in human peripheral blood lymphocytes, PLX2853 was considered positive for inducing structural aberrations in the 3-hour treatment without metabolic activation. In addition, statistically significant increases in numerical aberrations (polyploidy or endoreduplication) were noted in PLX2853-treated cultures after 3 hours of treatment without metabolic activation.

In a preliminary assessment of photo safety, PLX2853 did not reduce the viability of 3T3 mouse fibroblasts with and without UV A exposure and was therefore concluded to have no phototoxic potential.

In exploratory in vitro studies, PLX2853 was not toxic to human hepatocytes in culture after either 24 or 72 hours of exposure (IC_{50} >50 μM) and did not reduce the viability of human HepG2 or 293T cells after either 24 or 72 hours with 10% fetal bovine serum (IC_{50} >50 μM), indicating that the metabolites of PLX2853 are not toxic to liver and kidney cells.

Additional detailed information regarding the nonclinical pharmacology and toxicology of PLX2853 can be found in the Investigator's Brochure.

1.5.4 Proposed Starting Dose for Study PLX124-03

As of 22 March 2021, in an ongoing dose escalation study of PLX2853 in subjects with advanced solid tumors (Study PLX124-01; NCT03297424), PLX2853 has been generally safe and well-tolerated in 46 subjects dosed at up to 120 mg/day with dose limiting toxicities (DLTs) experienced by 4 subjects, and evidence of efficacy at doses as low as 5 mg/day (Section 1.8.1). As of 22 March 2021, doses of up to 180 mg/day have been evaluated in 22 subjects with relapsed or refractory acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS) in Study PLX124-02 (NCT03787498), with 2 DLTs reported. As of 23 April 2021, 80 mg/day has been determined to be the recommended Phase 2 dose (RP2D) in both Study PLX124-01 and Study PLX124-02.

Available PLX2853 PK data from the 2 studies (N = 67) showed dose-dependent increases in exposures throughout the dose range tested (5 to 180 mg/day). After oral administration, PLX2853 exhibited a short terminal half-life and no significant accumulation at steady state. In addition, PLX2853 showed dose-dependent pharmacodynamic effect in modulating the expression of BET target genes in peripheral blood cells (see Figure 1 below). Significant and consistent PDx effect was first observed at 40 mg/day dose. The corresponding daily exposure ($AUC_{0\text{-}24}$ = ~2000 ng•hr/mL) defines the pharmacologically active exposure.

Subjects enrolled in 6 of the 10 cohorts in PLX124-01 and 3 of the 7 cohorts in PLX124-02 were administered the 5 mg strength tablets. The 20 mg strength tablet form was introduced later in both studies to reduce pill burden. The Day 1 and Day 15 PK for the 2 tablet strength formulations were comparable at the 120 mg/day dose (PLX124-01) and 80 mg/day dose (PLX124-02).

The proposed starting dose for PLX2853 monotherapy is 80 mg/day, the highest dose that has been cleared of DLTs in both solid tumor (PLX124-01) and AML/MDS (PLX124-02) patients. PLX2853 + carboplatin combination may have a different safety profile compared with PLX2853 single agent. To ensure adequate safety margin in the combination trial, a starting dose of PLX2853 40 mg/day is recommended in combination with carboplatin. Based on the PK, PDx, and safety results, the proposed starting doses of 80 mg/day for PLX2853 monotherapy and 40 mg/day for PLX2853 + carboplatin combination therapy are expected to be pharmacologically active and safe.

1.6 Study Rationale

BET inhibitors such as PLX2853 have shown efficacy preclinically in multiple tumor types, including ovarian cancer (Yokoyama 2016; Zhang 2016; Zhu 2016). In ovarian cancer, BRD4 is often amplified and correlates with worse overall and disease-free survival (Zhang 2016; Zhu 2016; Goundiam 2015). Recently BET inhibitors have demonstrated the ability to delay the onset of resistance to standard-of-care cisplatin treatment in ovarian cancer cell lines and tumors (Yokoyama 2016). BET inhibitors have been shown to overcome chemoresistance by suppressing stem cell-like phenotypes. It is likely ovarian cancer stem-like cells contribute to the emergence of chemoresistance (Pylvas-Eerola 2016), suggesting that BET inhibition could be

used in a combination setting in patients with ovarian cancer to overcome resistance to platinum-based therapies.

Inactivating mutations of ARID1A, a core component of the SWI/SNF complex, have been found in various types of cancer and occur at high frequency in gynecological malignancies including ovarian clear cell adenocarcinoma (OCCC) and endometrioid adenocarcinoma. Recently it has been shown that small molecule inhibitors of BET specifically inhibit proliferation of ARID1A mutated OCCCs, both in vitro and in vivo due to a lethal interaction between BRD2 and ARID1A (Berns 2018; Helming 2014; Kelso 2017). BET inhibition may represent a novel treatment strategy for gynecological cancers harboring ARID1A loss of function mutations.

1.7 Potential Risks and Benefits

The identified risks of treatment with BET inhibitors from preclinical experience and other clinical development programs are hematologic toxicities, including thrombocytopenia, and decreased white blood cell and red blood cell counts. Decrease of lymphatic tissue and lymphocytes may also contribute to increased risk of infection. Intestinal mucosal atrophy was observed with mucosal inflammation and hemorrhage as a possible consequence. Prolongation of coagulation times (aPTT, prothrombin time) was also observed nonclinically and lung inflammation with hemorrhage was reported. Testicular atrophy was also reported in nonclinical studies. In the nonclinical toxicology studies, following 28 days of treatment-free recovery, microscopic findings had either completely resolved or were considered to be in the process of resolving, demonstrating the potential for reversibility of these findings. Most of these parameters can be monitored for their appearance and followed in clinical studies. This study is intended to evaluate safety, PK, tolerability, and preliminary efficacy of PLX2853 as a single agent and in combination with carboplatin. Subjects with no known treatment options have the opportunity to receive an experimental treatment with the hope of clinical benefit.

As of 22 March 2021, a total of 68 subjects have received PLX2853 at doses ranging from 5 to 180 mg in Studies PLX124-01 and PLX124-02. No treatment-related deaths have been reported. In PLX124-01, 4 treatment-related serious adverse events (SAEs) (thrombocytopenia, embolism, ischemic stroke, and subarachnoid hemorrhage) were reported in 1 subject at a dose of 120 mg/day. Two additional treatment-related SAEs of vomiting (120 mg/day) and diabetic ketoacidosis (60mg twice daily (BID)) were reported (the Sponsor determined that diabetic ketoacidosis was unrelated). In PLX124-02, 4 treatment-related SAEs have been reported. One subject experienced asymptomatic sinus bradycardia with sinus arrhythmia (80 mg/day) requiring overnight observation that resolved without treatment. Three subjects experienced a treatment-related SAE of hyperbilirubinemia. All 3 subjects were being treated above the RP2D (2 subjects dosed at 140 mg/day; 1 subject dosed at 180 mg/day).

As of 22 March 2021, the most common adverse events (AEs) associated with PLX2853 reported in >10% of subjects are nausea, fatigue, diarrhea, decreased appetite, dysgeusia, anemia, hyperbilirubinemia, and vomiting. Less common side effects associated with PLX2853 recorded

in 5% to 10% of subjects are dehydration, dizziness, dry mouth, gastroesophageal reflux disease, decreased platelet count, hyponatremia, increased aspartate aminotransferase, and white blood cell count decreased.

As of 22 March 2021, 1 DLT has been reported in Study PLX124-03: Grade 3 hyponatremia at a dose of 80 mg/day PLX2853 + carboplatin AUC 5 (mg•min/mL). Four DLTs have been reported in Study PLX124-01: 2 events of Grade 4 thrombocytopenia at 120 mg/day PLX2853; 1 dose reduction in Cycle 1 for ≥Grade 2 AE (Grade 3 fatigue, Grade 2 cheilitis, Grade 2 nausea) at 40 mg BID (80 mg total/day); and 1 dose reduction in Cycle 1 for ≥Grade 2 AE (Grade 3 thrombocytopenia) at 60 mg BID (120 mg total/day). Two DLTs have been reported in Study PLX124-02: Grade 3 hyperbilirubinemia at a dose of 180 mg/day; Grade 4 hyperbilirubinemia at a dose of 140 mg/day.

Refer to the Reference Safety Information section of the Investigator's Brochure for additional safety information.

1.8 Previous Human Experience

1.8.1 Interim Results of Study PLX124-01

As of 22 March 2021, 46 subjects were enrolled and treated at doses ranging from 5 to 120 mg/day, all in the dose escalation portion of Study PLX124-01 as an ongoing study of PLX2853 in subjects with advanced malignancies and were included in the PK populations. Cohort 1 (3 subjects), Cohort 2 (3 subjects), Cohort 3 (4 subjects), Cohort 4 (3 subjects), Cohort 5 (4 subjects), and Cohort 6 (3 subjects) have been dosed at 5, 10, 20, 40, 80, and 120 mg/day PLX2853, respectively, all with the 5 mg strength tablets. Cohort 7 (9 subjects), Cohort 8 (6 subjects), Cohort 9 (4 subjects), and Cohort 10 (6 subjects) have been dosed at 120 mg QD, 40 mg BID (80 mg total/day), 60 mg BID (120 mg total/daily), and 100 mg QD PLX2853, respectively, all with the 20 mg strength tablets. The total number of subjects in Study PLX124-01 with PK data and included in the PK analysis is 45 subjects.

The Day 1 and Day 15 geometric mean PK parameters are summarized in Table 4. After oral administration up to 120 mg/day PLX2853, rapid absorption was observed with median T_{max} values ranging from 0.5 to 2 hour. Dose-dependent increases in the geometric mean AUC_{0-24} values were observed on Day 1 and Day 15 (steady-state). No significant accumulation of PLX2853 was observed, which is consistent with the short terminal $T_{1/2}$ observed on Day 1 with values <3 hours. Subjects enrolled in Cohorts 1–6 were administered the 5 mg strength tablets. As dose escalation continued, high pill burden increasingly became a challenge for the subjects, which prompted the development of the 20 mg strength tablet. Subjects enrolled in Cohorts 7–10 were administered the 20 mg strength tablets. The Day 1 and Day 15 PK for the 20 mg strength tablets were compared to those for the 5 mg strength tablets at the 120 mg/day dose (Cohorts 6 and 7). The Day 1 exposures (AUC_{0-24}) are comparable between the 2 tablet formulations. Because of the small sample size, the statistical significance of the difference could not be assessed.

Table 4: Study PLX124-01: Geometric Means of Pharmacokinetic Parameters at Day 1 and Day 15 (Steady-state) After Oral Administration of 5, 10, 20, 40, 80, 120, and 120 (20 mg strength tablet) mg/day PLX2853 to Solid Tumor Patients

Dose [a] (mg/day)	Cohort	N	Geometric Mean [b]								
			Day 1				Day 15				Accumulation Ratio [c]
			T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	$T_{1/2}$ (hr)	
5	1	3	1.0	43.9	65.4	0.582	0.5	71.7	88.6	0.592	1.4
10	2	3	0.5	157	207	0.667	0.5	204	264	0.866	1.3
20	3	4	0.5	364	701	1.52	1.0	353	663	2.06	0.9
40	4	3	1.0	1260	2330	1.52	1.0	1330	2630	2.59	1.1
80	5	4	1.0	1470	2250	1.87	1.0	1700	2640	2.32	1.2
120	6	3	0.5	4400	6710	2.48	0.5	4390	5850	2.67	0.9
120	7	9/3[d]	1.0	2990	8770	2.50	1.0	4000	10500	4.32	1.5
40 BID (80 mg total)	8	6	1.0	519	2140	1.37	1.9	256	1270	1.41	0.6
60 BID (120 mg total)	9	4	1	914	4260	1.68	1.5	881	3420	1.68	0.8
100	10	6	1.5	2210	6630	2.02	2	1370	3660	1.63	0.6

AUC_{0-24} = area under the concentration-time curve from time 0 to 24 hours postdose; BID = twice daily; C_{max} = maximum observed concentration; T_{max} = time to maximum observed concentration; $T_{1/2}$ = terminal half-life

[a] Subjects in Cohorts 1-6 received 5 mg strength tablets; subjects in Cohorts 7-10 received 20 mg strength tablets.

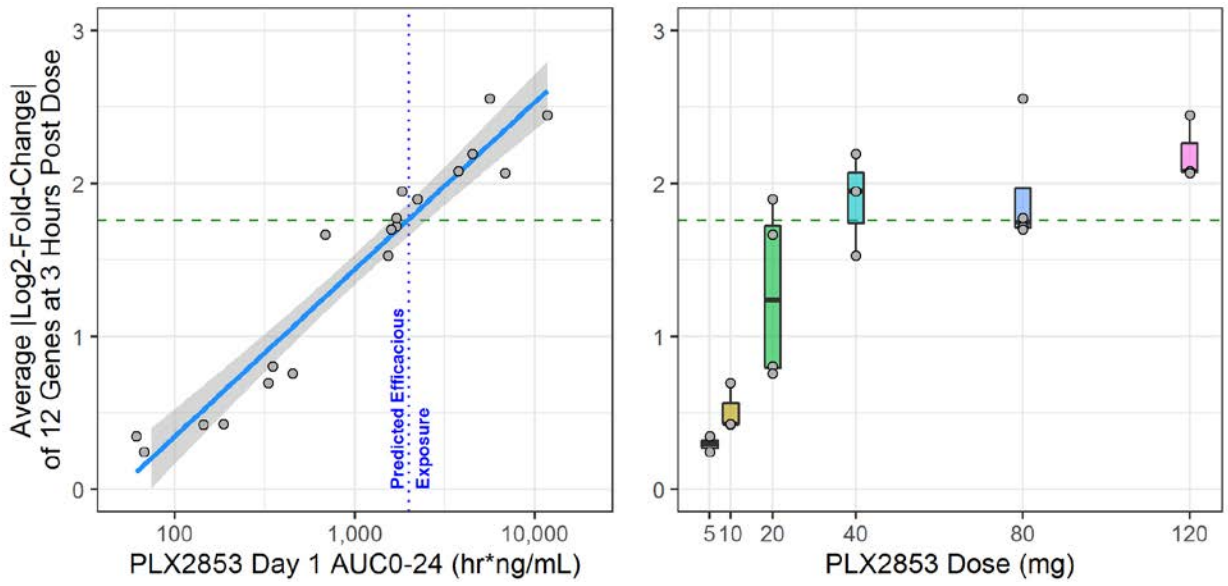
[b] T_{max} values presented are medians.

[c] Accumulation ratio values were calculated by dividing the AUC_{0-24} on Day 15 by the AUC_{0-24} on Day 1.

[d] N = 9 on Cycle 1 Day 1; N = 3 on Cycle 1 Day 15.

Analysis of peripheral blood cells on Day 1 (before and after a single dose of PLX2853) demonstrated dose- and exposure-dependent changes in the expression of BET target genes (Figure 1). PDx effect was as measured by a 12-gene BET inhibitor responsive signature (the 12 genes were: HEXIM1, WDR47, GLS, G3BP1, CALM11, CIRBP, CCR1, CCR2, TNFRSF8, SCIMP, BTN3A2, and KMO). Significant and consistent PDx effect was first observed at 40 mg/day QD. The corresponding daily exposure at steady-state at 40 mg/day (AUC_{0-24} = 2630 ng•hr/mL) defines the pharmacologically active exposure.

Figure 1: Study PLX124-01: PLX2853 Pharmacodynamic Effect on Peripheral Blood Cells



Of the subjects enrolled as of 22 March 2021, 34 were evaluable for efficacy. One subject with diffuse large B-cell lymphoma achieved a CR in the target tumor. Duration of response (DOR) is >10 months. One subject with ocular melanoma achieved a partial response (PR) as the best response in the target tumor. DOR was 92 days. Nineteen subjects experienced stable disease (SD) as the best response in the target tumor. One subject with ARID1A-mutant primary peritoneal cancer who had a best response of SD had an unconfirmed PR at Cycle 11 (30 weeks). The other 12 subjects experienced progressive disease (PD).

1.8.2 Interim Results of Study PLX124-02

As of 22 March 2021, 22 subjects have enrolled in PLX124-02 at doses ranging from 20 to 180 mg/day. Cohort 1 (3 subjects), Cohort 2 (4 subjects), and Cohort 3 (3 subjects) received 20, 40, and 80 mg/day PLX2853, respectively, all with the 5 mg strength tablets. Cohort 4 (3 subjects), Cohort 5 (3 subjects), Cohort 6 (2 subjects), and Cohort 7 (4 subjects) have been dosed at 80, 140, 180, and 140 mg/day PLX2853, respectively, all with the 20 mg strength tablets.

The Day 1 and Day 15 geometric mean PK parameters are summarized in Table 5. After 20, 40, 80, 140, and 180 mg/day PLX2853, rapid absorption was observed with median T_{max} values ranging from 0.71 to 1.73 hour (Table 5). Two subjects in the 20 mg/day cohort (Cohort 1) had higher exposures on Cycle 1 Day 15 compared to Cycle 1 Day 1; the increases in PLX2853 concentrations were attributed to patient-specific conditions unrelated to PLX2853. Once these conditions improved, PLX2853 plasma concentrations returned to expected levels. Dose-dependent increases in the geometric mean AUC_{0-24} values were observed on Day 1 (from

20 to 180 mg/day) and Day 15 (from 40 to 180 mg/day) (steady-state). No significant accumulation of PLX2853 was observed from 40 to 180 mg/day, which is consistent with the short terminal $T_{1/2}$ observed on Day 1 with values <3.5 hours (Table 5). The Day 1 and Day 15 PK parameters for the 2 strength tablet formulations (5 mg and 20 mg strength tablets) were compared at the 80 mg/day dose (Cohorts 3 and 4). The geometric mean AUC_{0-24} values are comparable.

Table 5: Study PLX124-02: Geometric Means of Pharmacokinetic Parameters at Day 1 and Day 15 (Steady-state) After Oral Administration of 20, 40, 80, and 80 (20 mg strength tablet) mg/day PLX2853 to AML Patients

Dose [a] (mg/day)	Cohort	N	Geometric Mean [b]								
			Day 1				Day 15				Accumulation Ratio [c]
			T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	$T_{1/2}$ (hr)	
20	1	3	1	243	676	1.92	1	390	1400	2.39	2.1
40	2	4	0.75	648	1080	1.38	0.5	565	836	2.08	0.8
80	3	3	1	1530	2740	2.07	1	1630	2700	2.05	1.0
80	4	3	1	1330	3020	1.95	1	1040	2450	2.04	0.8
140	5	3	0.71	1390	2550	1.77	1	2640	4990	1.74	3.6
180	6	2	1	3480	12000	3.48	1	6190	11200	2.20	0.9
140	7	4/2[d]	1.68	1490	5690	2.85	1.73	1450	3840	1.75	0.7

AML = acute myeloid leukemia; AUC_{0-24} = area under the concentration-time curve from time 0 to 24 hours postdose; C_{max} = maximum observed concentration; T_{max} = time to maximum observed concentration; $T_{1/2}$ = terminal half-life

[a] Subjects in Cohorts 1-3 received 5 mg strength tablets; subjects in Cohorts 4-7 received 20 mg strength tablets.

[b] T_{max} values presented are medians.

[c] Accumulation ratio values were calculated by dividing the AUC_{0-24} on Day 15 by the AUC_{0-24} on Day 1.

[d] N = 4 on Cycle 1 Day 1; N = 2 on Cycle 1 Day 15.

2.0 STUDY OBJECTIVES

2.1 Phase 2a (PLX2853 Monotherapy)

The primary objective is as follows:

- To evaluate the efficacy of single-agent PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation

The secondary objectives are as follows:

- To further characterize the safety and efficacy of single-agent PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation
- To further evaluate the PK of PLX2853

2.2 Phase 1b (PLX2853 + Carboplatin Combination)

The primary objective is as follows:

- To evaluate the safety and tolerability of PLX2853 + carboplatin combination including DLTs, MTD, and RP2D in subjects with platinum-resistant EOC

The secondary objective is as follows:

- To characterize the PK and efficacy of PLX2853 when combined with carboplatin in subjects with platinum-resistant EOC

2.3 Phase 2a (PLX2853 + Carboplatin Combination)

The primary objective is as follows:

- To evaluate the efficacy of PLX2853 + carboplatin combination at the RP2D in subjects with platinum-resistant EOC

The secondary objective is as follows:

- To further characterize the safety and PK of PLX2853 when combined with carboplatin in subjects with platinum-resistant EOC

2.4 All Phases

The exploratory objectives are as follows:

- To assess biomarkers in peripheral blood cells, tumor cells, and tissue biopsies
- To further evaluate the PDx of PLX2853

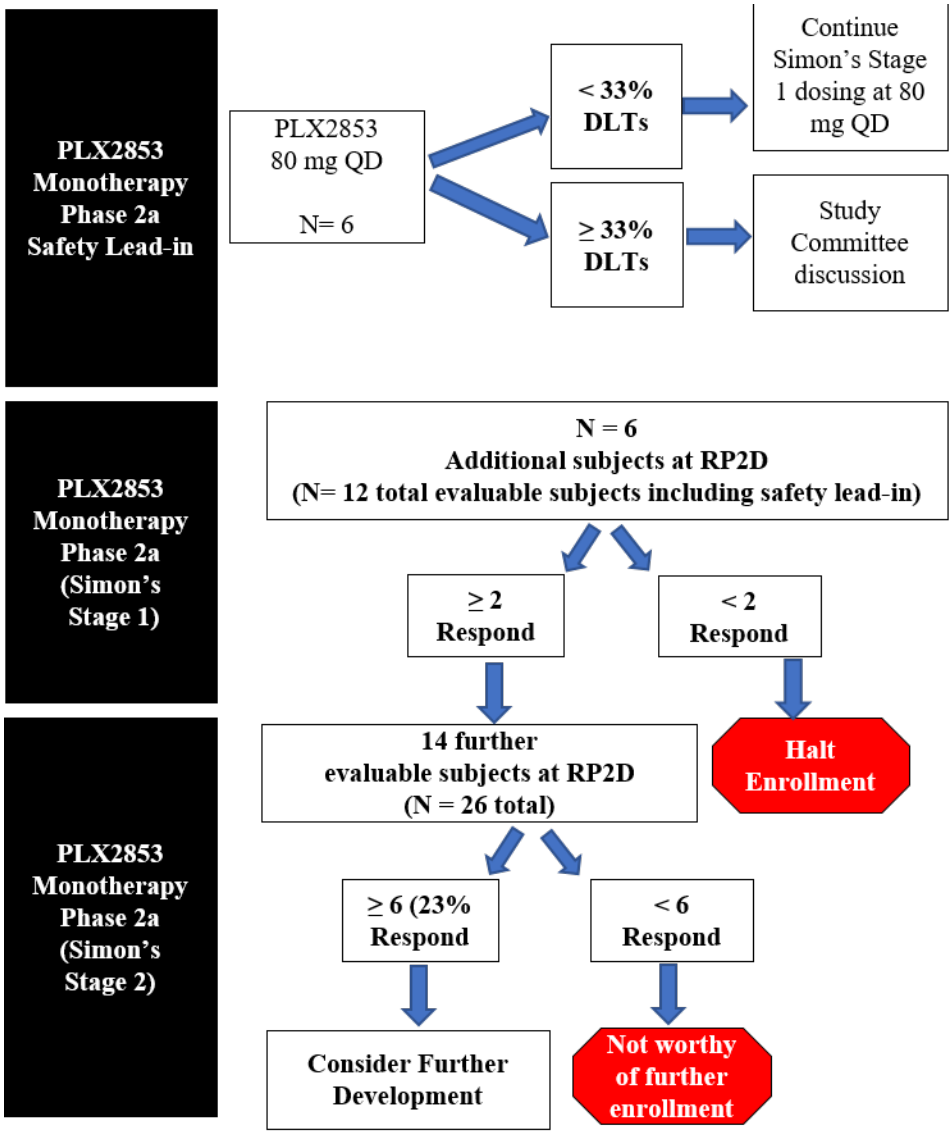
3.0 STUDY DESIGN

3.1 Overview of Study Design

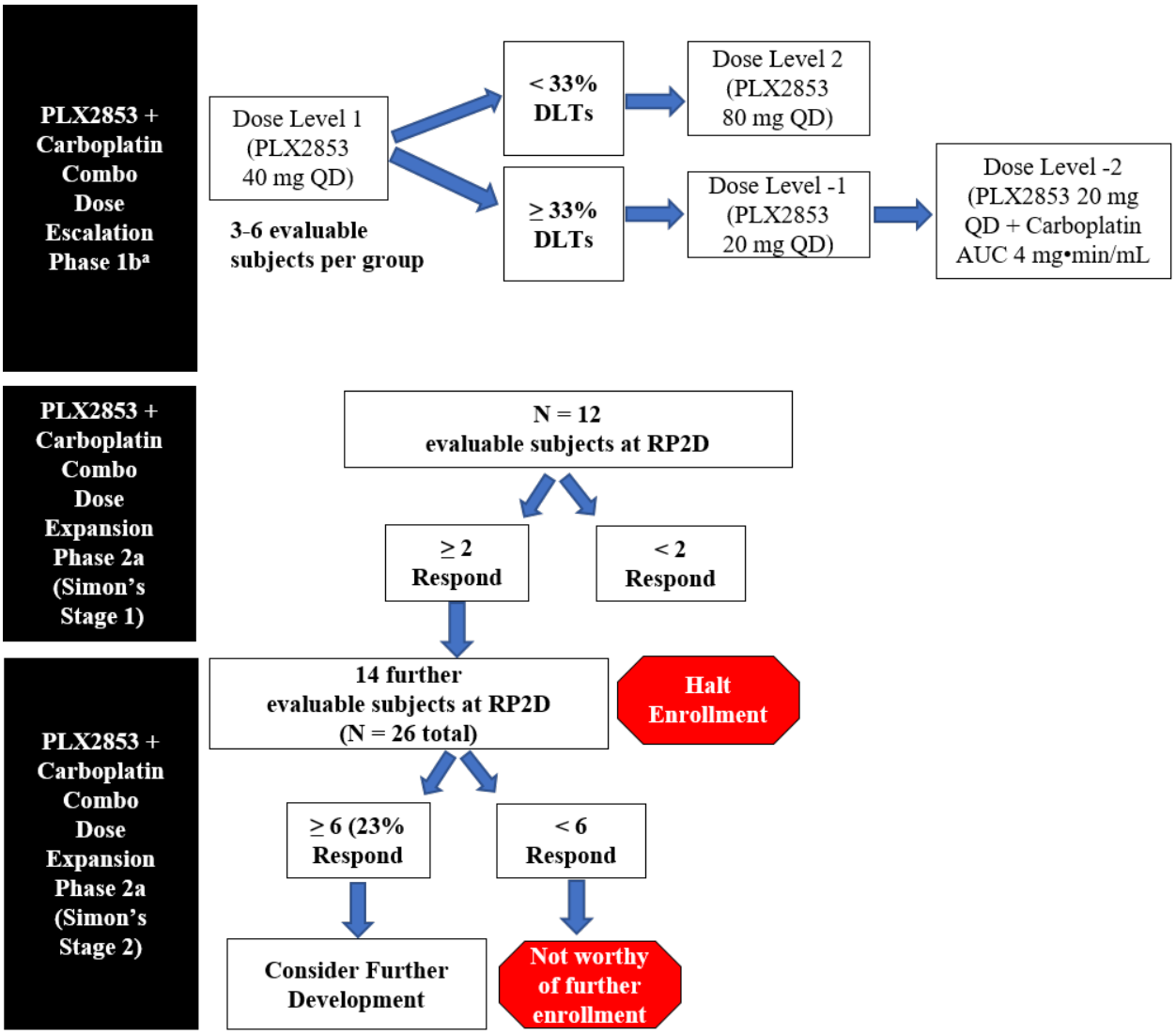
This open-label, multicenter, 2-part study will evaluate in parallel PLX2853 monotherapy in subjects with advanced gynecological malignancies with a known ARID1A mutation (with and without PIK3CA, PI3KR1, and/or PTEN mutations) and PLX2853 + carboplatin combination therapy in subjects with platinum-resistant EOC (including fallopian tube or primary peritoneal cancer) (Figure 2).

Figure 2: Overview of Study PLX124-03

PLX2853 Monotherapy Study Design:



PLX2853 + Carboplatin Combination Study Design



AUC = area under the concentration-time curve; DLT = dose-limiting toxicity; EOC = epithelial ovarian cancer; QD = once daily; RP2D = recommended Phase 2 dose

[a] All carboplatin doses are target AUC of 5 mg•min/mL unless otherwise specified.

Note: Alternative scheduling of PLX2853 administration may be evaluated

3.1.1 Phase 2a PLX2853 Monotherapy Design

The Phase 2a monotherapy part of the study will evaluate the efficacy, safety, PK, and PDx of PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation using a Simon's 2-stage design. ARID1A, PIK3CA, PIK3R1, PTEN and homologous recombination repair mutational status and homologous recombination deficiency status will be determined based on historical data for all potential subjects from a commercially available next generation sequencing (NGS) panel such as FoundationOne® CDx or a local NGS panel performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.

The safety lead-in will comprise 6 subjects who will be enrolled at a dose of 80 mg/day and assessed for safety by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and for evidence of DLTs. The rules for determining DLT are defined further below. After the safety lead-in has been completed, the Study Committee will convene to evaluate safety, PK, and PDx data to determine which dose to take forward for the remainder of subjects in Phase 2. Response rate for subjects in the safety lead-in will be included in the efficacy analysis for the purpose of the Simon's 2 stage design.

The starting dose level of PLX2853 will be 80 mg/day. In the absence of a DLT and in conjunction with review of the PK and PDx data from each cohort by the Study Committee, the safety lead-in is planned to occur in the following manner:

- The starting dose of PLX2853 will be 80 mg/day
- DLTs will be assessed in the first 28-day treatment period/cycle

After dosing has been completed in this cohort of subjects, safety, PK, and PDx data (as applicable) will be reviewed, and any dose modification decisions, if applicable, will be made by the Study Committee. If ≥33% DLTs are seen during the initial safety lead-in, the Safety Committee will convene to consider a dose reduction. If a dose reduction is deemed appropriate, the subjects in the initial safety lead-in will need to be replaced and a repeat 6 subject safety lead-in will need to be conducted at this lower dose. Dose modification decisions will also take into consideration safety information beyond the DLT period from all enrolled subjects. If no DLT is observed, the recommended dose for further evaluation may be established based on safety, PK, and PDx convenience of dosing in subjects treated at that dose. If a DLT is seen in ≥33% of subjects in the safety lead-in then the Study Committee will convene to consider alternative dose levels and schedule.

If a subject misses more than 25% of the doses for Cycle 1 (e.g., >7 doses of PLX2853 in 28 days) during the DLT window period for reasons other than an AE, additional subject(s) may be enrolled to provide adequate data for safety assessments.

PLX2853 PK data will be analyzed for C_{max}, plasma concentration-time curve (AUC), and accumulation ratio at steady state and compared with prior dose levels. Dose adjustments may also require increasing the number of subjects within a subset of subjects at a given dose level as a result of the review of safety, observed or anticipated disease activity, and PK data.

A subset of patients may be studied in this trial to assess the effect of food on PLX2853 exposure. These subjects will receive a single dose of PLX2853 under fed conditions 3 or 4 days prior to Cycle 1 Day 1 and have serial PK samples collected. On Cycle 1 Day 1, subjects will commence dosing at the same dose level under fasted conditions.

At the discretion of the Sponsor, an additional Phase 2a monotherapy cohort may be enrolled using a Simon's 2 stage design to evaluate the efficacy, safety, PK, and PDx of PLX2853 in subjects with advanced gynecological malignancies with a known ARID1A mutation and who do

not have known pathogenic mutations in the following genes (unless allowed with Medical Monitor approval):

- Mutations or amplifications in PIK3CA
- Mutations or amplifications in PIK3R1
- Mutations or deletions in PTEN

3.1.2 Phase 1b/2a PLX2853 + Carboplatin Combination

The Phase 1b/2a combination part of the study will evaluate the safety, PK, PDx, and efficacy of PLX2853 in combination with carboplatin in subjects with platinum-resistant EOC.

In Phase 1b (dose escalation), the safety profile, RP2D/MTD, PK, PDx, and preliminary efficacy of PLX2853 (administered orally in 28-day treatment cycles) in combination with carboplatin (administered IV on Day 1 of each 28-day cycle) will be evaluated. Each cohort will be enrolled and assessed using a standard "3+3" design. The rules for determining DLTs and dose escalation are defined in Section 6.1 and Section 5.3.1, respectively.

The provisional dose escalation plan is detailed in Table 6.

Table 6: Provisional Dose Escalation Plan

Dose Level	Combination PLX2853 Dose (mg/day)[a]	Carboplatin Dose (mg•min/mL)[b]
-2	20	AUC 4
-1	20	AUC 5
1 (Starting Dose)	40	AUC 5
2	80	AUC 5

AUC = area under the concentration-time curve

[a] Once daily dosing schedule unless otherwise specified.

[b] Dosed on Day 1 of each 28-day cycle.

In Phase 1b combination, the starting dose level of PLX2853 will be 40 mg/day plus a target AUC of 5 mg•min/mL dose of carboplatin (Cohort 1). In the absence of a DLT in the first cycle of treatment and in conjunction with review of the PK and available PDx data from each cohort by the Study Committee, dose escalation is planned to occur in the following manner:

- DLTs will be assessed in the first treatment cycle (up to carboplatin dosing on Cycle 2 Day 1).
- The starting dose of PLX2853 will be 40 mg/day (Cohort 1), which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day.

- Carboplatin will be administered using a target AUC of 5 mg•min/mL on Day 1 of each 28-day treatment cycle per label. Carboplatin must be given within 7 days of Cycle 2 Day 1 (delays due to reasons other than toxicity will not be assessed as a DLT).
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be investigated. If that dose level is intolerable, Dose Level -2 (PLX2853 20 mg/day and carboplatin AUC 4 mg•min/mL) will be studied. If that dose level is intolerable, the study will be halted.
- In the absence of a DLT, a second cohort with a PLX2853 dose of 80 mg/day will be investigated (Cohort 2).

A minimum of 3 to 4 subjects will be initially enrolled in Cohort 1. If a DLT is observed in 1 subject in a given cohort, up to 6 subjects will be treated at that dose. If DLTs are observed in 2 or more of 6 subjects (or ≥33% of the cohort) at a dose level, the dose at which this occurs will be considered intolerable and the MTD will have been exceeded. The highest dose level at which 0 of 3 subjects or 0 or 1 of 6 subjects experience a DLT will be declared the RP2D. If 3 to 4 subjects were initially evaluated at that dose level, an additional 2 to 3 subjects may be enrolled to evaluate for DLTs at that dose level for confirmation. Up to 6 additional subjects with a known ARID1A mutation (unless otherwise approved by the Medical Monitor) may be treated at the RP2D at the discretion of the Sponsor for dose confirmation purposes.

In order to be DLT evaluable a subject must not have missed more than 25% of study drug for reasons other than AE and must not have missed receiving carboplatin within 7 days of Cycle 2 Day 1 (if applicable) for reason other than AE. If a subject misses more than 25% of the doses for Cycle 1 (e.g., >7 doses of PLX2853 in 28 days) during the DLT window for reasons other than an AE, additional subject(s) may be enrolled to provide adequate data for dose escalation decision making. Subjects who do not complete Cycle 1 for reasons other than drug toxicity may be replaced. Subjects must receive their Cycle 2 Day 1 carboplatin dose to be considered evaluable unless the reason for missing carboplatin is due to an AE.

Once all ongoing subjects in a dose cohort have been treated for at least 2 cycles and the safety and tolerability of that dose level has been established, intra-subject dose escalation to that dose level may be permitted for subjects enrolled at lower dose levels who have not experienced an unresolved Grade 3 or higher treatment-related toxicity and have completed 2 cycles. Any intra-subject dose escalation requires a discussion and agreement with the Medical Monitor.

After dosing has been completed in each cohort, safety, PK, and PDx data (if available) will be reviewed, and dose escalation decisions will be made by the Study Committee. Dose escalation decisions will also take into consideration safety information beyond the DLT period from earlier cohorts. If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, convenience of dosing, and PDx (if available) in subjects treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days. PLX2853 and carboplatin may not be dose escalated in the same cycle.

PLX2853 PK data will be analyzed in each dosing cohort for C_{max}, AUC, and accumulation ratio at steady state and compared with prior dose levels. The number of subjects at a given dose level may be increased as a result of the review of safety, observed or anticipated disease activity, and PK data. Additional dosing schedules may be studied, such as alternate day dosing (e.g., every other day) depending on emerging safety and PK data.

In Phase 2a (dose expansion), efficacy as well as additional safety, PK, and PDx data of PLX2853 in combination with carboplatin at the RP2D dose established in Phase 1b by the Study Committee will be obtained using a Simon's 2-stage design.

3.2 Number of Subjects

Up to 85 evaluable subjects may be enrolled across the study.

Phase 2a (PLX2853 monotherapy):

There will be up to 2 Simon's 2-stage design cohorts of up to 38 evaluable subjects with ARID1A mutation-positive (with and without PIK3CA, PIKR1, and/or PTEN mutations) advanced gynecological malignancies. The safety lead-in of 6 subjects dosed at the level selected for Phase 2a will be included in the group of 12 evaluable subjects for Stage 1.

Phase 1b (PLX2853 + carboplatin combination):

Approximately 9 to 15 evaluable subjects with platinum-resistant EOC will be enrolled, depending on the number of escalation cohorts investigated. Up to 6 additional subjects with a known ARID1A mutation (unless otherwise approved by the Medical Monitor) may be treated at the RP2D at the discretion of the Sponsor for dose confirmation purposes.

Phase 2a (PLX2853 + carboplatin combination):

There will be 1 Simon's 2-stage design cohort of between 12 to 26 evaluable subjects with platinum-resistant EOC.

3.3 Duration of Study

The study encompasses the following periods:

- **Screening Period:** Up to 28 days prior to the first dose of study drug
- **Treatment Period:** Daily in 28-day cycles until subject discontinuation or withdrawal or study termination (see Section 7.1.5)
  - Subjects participating in the optional Food Effect sub-study will take a single dose of PLX2853 3 or 4 days prior to C1D1.

  - For subjects enrolled in either the monotherapy or combination therapy cohorts, further treatment with either PLX2853 and/or carboplatin will depend on tolerability and clinical benefit as described in Section 7.1.5. In general, for subjects receiving the combination of PLX2853 + carboplatin, it is estimated that subjects will be treated with carboplatin for up to 6 cycles.

- **30-day Follow-up (FU) Visit:** Approximately 30 days after the last dose of study drug or prior to starting any new anti-cancer therapy, whichever occurs first
- **Long-term Follow-up Period:** Survival follow-up can be via clinic visit, phone call to the subject or referring physician, or other method deemed appropriate by the site and should assess survival, progression, subsequent therapy, and response. Subjects will be followed until death, withdrawal of consent, or loss to follow-up according to the following schedule:
  - First 2 years after the 30-day FU Visit – Every 3 months
  - Third year after the 30-day FU Visit and beyond – Every 6 months
  - Any subject with a confirmed response who discontinues treatment for reasons other than disease progression will continue to be followed per standard of care and no less than every 3 months until documented disease progression, initiation of a new anti-cancer treatment, or 1 year from discontinuation of study treatment. Radiographic scan data will be collected and if scan data are not available, a scan will be obtained every 3 months until 6 months of radiographic follow-up after confirmed response has been obtained.

3.4 Study Endpoints

3.4.1 Primary Endpoints

The primary endpoints are as follows:

- Phase 2a (PLX2853 monotherapy): overall response rate (ORR) as measured by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- Phase 1b (PLX2853 + carboplatin combination): establish the MTD/RP2D for the combination of PLX2853 + carboplatin
- Phase 2a (PLX2853 + carboplatin combination): ORR as measured by RECIST v1.1

3.4.2 Secondary Endpoints

The secondary endpoints are as follows:

- Incidence of treatment-emergent adverse events (TEAEs), changes in safety parameters, and unacceptable toxicities

- DOR
- Disease control rate (DCR)
- Progression-free survival (PFS)
- Overall survival (OS)
- PLX2853 PK parameters following single and repeated dosing

3.4.3 Exploratory Endpoints

The exploratory endpoint is as follows:

- Analysis of peripheral blood and tumors for dose- and exposure-dependent changes in the expression of BET target genes

3.5 Randomization

None of the subjects in this study will be randomized.

4.0 STUDY POPULATION

Subjects must meet the following inclusion and exclusion criteria to be enrolled in the study.

4.1 Inclusion Criteria

1. Age ≥18 years at the time of signing informed consent
2. Histologically or cytologically confirmed diagnosis of 1 of the following and must have measurable disease per RECIST v1.1:

- **Phase 2a (PLX2853 monotherapy):** Any advanced gynecological malignancy (cervical, vaginal, vulvar, uterine, ovarian, fallopian tube, or primary peritoneal) with a known ARID1A mutation, that is intolerant to or refractory to all standard therapy known to confer clinical benefit.
  - Subjects must have tumor accessible for sequential biopsy and be willing to provide on-study tumor tissue biopsy (core needle biopsy or excision required). Tissue collection must not constitute a significant risk procedure. A significant risk procedure is generally considered to be one for which the procedure associated absolute risk of mortality or major morbidity in the patient's clinical setting and at the institution completing the procedure is 2% or higher. When possible, newly obtained tissue should be collected from a non-target lesion.
- **Phase 1b and Phase 2a (PLX2853 + carboplatin combination):**

  Platinum-resistant EOC (including fallopian tube or primary peritoneal cancer). Platinum-resistant is defined as disease that may have responded to a platinum-containing chemotherapy regimen, but there is documentation of demonstrated recurrence within 6 months following the completion of that platinum-containing regimen.

  OR

  Subjects with platinum-refractory EOC are eligible, provided refractory outcome was to second line or later repeated platinum regimen (not first line). Refractory is defined as disease that failed to achieve at least a PR to a platinum-containing regimen (i.e., SD or actual disease progression).

  Progressive disease of EOC following platinum-based therapy can be documented by physical examination, computed tomography (CT) scans, or a doubling of cancer antigen 125 (CA-125) levels from either 1) upper limit of normal (ULN) or 2) most recent nadir value (per the Rustin criteria [Rustin 2011] [Appendix 6]). For CA-125 to be used as a criterion for progressive disease, the CA-125 level nadir must have been above the ULN. In addition, the CA-125 nadir level must have been confirmed by a second measurement at least 1 week after the initial measurement.

  - Subjects in Phase 2a must have tumor accessible for sequential biopsy and be willing to provide on-study tumor tissue biopsy (core needle biopsy or excision required). Tissue collection must not constitute a significant risk procedure. A significant risk procedure is generally considered to be one for which the procedure associated absolute risk of mortality or major morbidity in the patient's clinical setting and at the institution completing the procedure is 2% or higher. When possible, newly obtained tissue should be collected from a non-target lesion.

3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1
4. Adequate organ function as demonstrated by the following laboratory values. All Screening laboratory tests should be performed within 10 days of the first PLX2853 dose. Subjects must meet the following eligibility criteria prior to dosing:

- Hematological:
  - Neutrophils ≥1500/µL
  - Platelets ≥100,000/µL
  - Hemoglobin ≥9 g/dL (transfusion and erythropoietin not permitted within 14 days prior to blood draw)
- Renal:
  - Estimated glomerular filtration rate (GFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine calculation [Appendix 1]) ≥60 mL/min/1.73 m^2
- Hepatic:
  - Serum total bilirubin ≤1.5 × ULN
    OR
  - Direct bilirubin ≤ULN for subjects with total bilirubin >1.5 × ULN

    Exception for elevated bilirubin secondary to Gilbert's disease, in which case it must be ≤2.5 mg/dL. Confirmation of Gilbert's diagnosis requires: elevated unconjugated (indirect) bilirubin values; normal complete blood count in previous 12 months, blood smear, and reticulocyte count; normal aminotransferases and alkaline phosphatase in previous 12 months
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN
  - Gamma-glutamyl transferase ≤3 × ULN
- Coagulation:
  - International normalized ratio ≤1.5 × ULN
  - aPTT ≤1.5 × ULN

- Chemistry:
  - Albumin ≥3.0 g/dL

5. Women of child bearing potential (defined as any female who has experienced menarche and who has not undergone successful surgical sterilization [hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or is not postmenopausal) must have a negative serum pregnancy test within 7 days prior to taking the first dose of study drug and, if sexually active, must agree to use a highly effective method of contraception (a contraception method with a failure rate <1% per year) and 1 additional barrier method from the time of the negative pregnancy test to 90 days (for subjects in the United States (US)) or 6 months (for subjects in Canada) after the last dose of study drug. Women of non-child bearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year.
6. Except as specified above for organ function, all drug-related toxicity from previous cancer therapy must be resolved (to Grade ≤1 or baseline per NCI CTCAE v5.0) prior to study treatment administration (Grade 2: alopecia, hot flashes, decreased libido, immuno-oncology drug induced hypothyroidism controlled with medication, or neuropathy is allowed).
7. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements

4.2 Exclusion Criteria

1. Prior exposure to a bromodomain inhibitor, such as OTX-015 or CPI-0610
2. Ongoing systemic infection requiring treatment with antibiotic, antiviral, or antifungal treatment
3. Autoimmune hemolytic anemia or autoimmune thrombocytopenia
4. Presence of symptomatic or uncontrolled central nervous system or leptomeningeal metastases (Note: Subjects with stable, treated brain metastases are eligible for this study. However, subjects must not have required steroid treatment for their brain metastases within 30 days of Screening.)
5. Red blood cell or platelet transfusion within 14 days of Screening blood draw
6. Known or suspected allergy to the investigational agent or any agent given in association with this study
7. Use of biotin (i.e., Vitamin B7) or supplements containing biotin higher than the daily adequate intake of 30 µg (NIH-ODS 2020). (Note: Subjects who switch from a high dose to a dose of 30 µg/day or less are eligible for study entry.) Use of herbal, alternative, and food supplements (i.e., PC-Spes, Saw Palmetto, St. John's Wort, etc.) and probiotics must be discontinued before treatment start. Daily multi-vitamin (provided it does not contain biotin >30 µg/day), calcium, and Vitamin D are permitted.

8. Use of strong inhibitors and inducers of CYP3A4 and 2C8 (Appendix 2)
9. Clinically significant cardiac disease, defined as any of the following:
    - Clinically significant cardiac arrhythmias including bradyarrhythmias and/or subjects who require anti-arrhythmic therapy (excluding beta blockers or digoxin). Subjects with controlled atrial fibrillation are not excluded.
    - Congenital long QT syndrome or subjects taking concomitant medications known to prolong the QT interval (drugs with a low risk of QTc prolongation that are needed for infection control or nausea may be permitted with approval from the Medical Monitor). A list of drugs known to prolong the QT interval and risk of Torsades de pointes can be found in Appendix 4.
    - QT interval corrected using Fridericia's equation (QTcF) ≥470 msec at Screening (based on average of triplicate electrocardiograms (ECGs) at baseline)
    - If the QTc is prolonged in a subject with a pacemaker or bundle branch block, the subject may be enrolled in the study if confirmed by the Medical Monitor
    - History of clinically significant cardiac disease or congestive heart failure >New York Heart Association Class II. Subjects must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months.
    - Uncontrolled hypertension, defined as systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg that has been confirmed by 2 successive measurements despite optimal medical management
    - Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within the 3 months before start of study medication (except for adequately treated catheter-related venous thrombosis occurring >1 month before the start of study medication)
10. Inability to take oral medication or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the Investigator, would preclude adequate absorption
11. Poorly controlled known Type 2 diabetes with HbA1C >7.5%
12. Non-healing wound, ulcer, or bone fracture
13. Infection with HIV-1 or HIV-2. **Exception:** subjects with well-controlled HIV (e.g., CD4 >350/mm^3 and undetectable viral load) are eligible.

14. Current active liver disease from any cause, including hepatitis A (hepatitis A virus immunoglobulin M positive), hepatitis B (hepatitis B virus [HBV] surface antigen positive), or hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV ribonucleic acid). Subjects with HCV with undetectable virus after treatment are eligible. Subjects with a prior history of HBV are eligible if quantitative PCR for HBV DNA is negative. Note that elevated levels of biotin may interfere with viral serology testing.
15. Active known second malignancy with the exception of any of the following:
    - Adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, or in situ cervical cancer
    - Adequately treated Stage I cancer from which the subject is currently in remission and has been in remission for ≥2 years
    - Any other cancer from which the subject has been disease-free for ≥3 years
16. Major surgery or significant traumatic injury within 28 days prior to Cycle 1 Day 1
17. Hospitalization for subacute bowel obstruction within 28 days prior to Cycle 1 Day 1
18. Receipt of anti-cancer therapy prior to Cycle 1 Day 1:
    - Chemotherapy, radiation therapy, or small molecule anti-cancer therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) of Cycle 1 Day 1
    - Immune therapy or other biologic therapy (e.g., monoclonal antibodies, antibody-drug conjugates) for the treatment of cancer within 21 days or 5 half-lives (whichever is shorter) of Cycle 1 Day 1

    Subjects can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 28 days prior to treatment with study drug.
19. Subject is participating in any other therapeutic clinical study (observational or registry studies are allowed).
20. Subjects who are pregnant or breast-feeding
21. Presence of any other medical, psychological, familial, sociological, or geographic condition potentially hampering compliance with the study protocol or would interfere with the study endpoints or the subject's ability to participate.

4.2.1 Effective Methods of Contraception

If sexually active, women of child bearing potential must agree to use a highly effective method of contraception (a contraception method with a failure rate <1% per year) and 1 additional barrier method from the time of the negative pregnancy test to 90 days (for subjects in the US) or 6 months (for subjects in Canada) after the last dose of study drug.

Barrier/Intrauterine Methods	Hormonal Methods
Male or female condom with or without spermicide Cap, diaphragm, or sponge each with spermicide Copper T intrauterine device or levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Implants[a] Hormone shot or injection[a] Combined pill[a] Patch[a]

[a] Highly effective (failure rate of <1% per year).

5.0 STUDY TREATMENT

5.1 Investigational Product

5.1.1 PLX2853

PLX2853 is formulated as 20 mg strength tablets for oral use. The active drug substance is PLX2853, with additional excipients of hypromellose acetate succinate, copovidone, microcrystalline cellulose, mannitol, croscarmellose sodium, silicon dioxide, sodium stearyl fumarate, sodium bicarbonate, and poloxamer. The drug product presentation is a white to off-white solid tablet. The tablets are embossed with "PLX" on one side.

5.1.2 Carboplatin

Carboplatin is supplied as a sterile, pyrogen-free 10 mg/mL aqueous solution of carboplatin, USP for injection.

The NCCN 2018 recommendations should be used for carboplatin dosing as follows:

The Calvert equation should be applied to calculate dosage using a target AUC in mg•min/mL:
Carboplatin dose (mg) = (target AUC) × (GFR + 25)

Target AUC will be 5 mg•min/mL. With the Calvert equation, the total dose of carboplatin is calculated in mg not mg/m^2. The GFR should be estimated by calculated creatinine clearance (CrCl) using the Cockcroft-Gault equation:

$$\text{CrCl (male; mL/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

CrCl (female; mL/min) = 0.85 × CrCl (male)

The dose of carboplatin for desired exposure (AUC) should be capped to avoid potential toxicity due to overdosing. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for subjects with normal renal function. Based on the Calvert equation, the maximum doses can be calculated as follows:

Maximum carboplatin dose (mg) = Target AUC (mg•min/mL) × (125 mL/min + 25)

For a target AUC = 5, the maximum dose is 5 × 150 = 750 mg
For a target AUC = 4, the maximum dose is 4 × 150 = 600 mg

For overweight or obese subjects (body mass index ≥25 kg/m^2), consider using an adjusted body weight:
Adjusted body weight (kg) = ideal body weight (IBW) + 0.4 × (total body weight – IBW)

For subjects with abnormally low serum creatinine, including elderly or cachectic subjects, consider using a minimum creatinine of 0.7 mg/dL to avoid overestimation of CrCl.

Once the initial dose of carboplatin is calculated, it does not need to be recalculated for subsequent cycles unless the subject is experiencing toxicity and requires dose modification to a lower dose of carboplatin.

5.2 Study Drug Administration

5.2.1 PLX2853 Administration

PLX2853 should be dosed orally with water using a tablet formulation as defined for each cohort. Subjects should fast for at least 2 hours before and 1 hour after taking PLX2853, except for PK collection days when subjects should fast for at least 8 hours (10 hours on fed dosing day for the optional Food Effect sub-study) before taking PLX2853 (see Section 5.2.3). During the fasting period, subjects may eat a low-fat snack (e.g., crackers, dry toast, etc.) if they experience gastrointestinal symptoms (e.g., nausea, vomiting, etc.) following dosing. PLX2853 should be taken at approximately the same time each day. PLX2853 should be swallowed whole and not crushed, chewed, or dissolved in water. A dosing period of up to 30 minutes is permissible if required by the number of tablets to be taken or as convenient for the subject. Missed doses (generally outside of a 2-hour dosing window for BID dosing and a 5-hour dosing window for QD dosing) should be skipped and not administered as a double dose at the next administration. Subjects who omit their dose should be instructed NOT to make up that dose. Doses that are vomited should not be replaced.

Subjects will be treated with PLX2853 for 28-day cycles. Guidance for dose modification is in Section 6.2.

5.2.2 Carboplatin Administration

For subjects enrolled to the Phase 1b/2a PLX2853 + carboplatin cohorts, carboplatin will be administered intravenously using a target AUC of 5 mg•min/mL on Day 1 of each 28-day treatment cycle per the label. Carboplatin should be administered at least 2 hours after PLX2853 dosing. Prophylaxis for hypersensitivity reaction and skin testing should be considered per institutional standard of care for subjects who have received prior platinum-based regimens. Details on carboplatin dosage calculation is in Section 5.1.2. Guidance for dose modification is in Section 6.2.

5.2.3 Dosing on Pharmacokinetic Sample Collection Days

Subjects should be instructed *not* to take their morning dose of PLX2853 at home before the clinic visit. The time of dosing will be recorded in the clinic. On PK days where a full PK profile is collected (e.g., C1D-3 or C1D-4 (as applicable) C1D1, C1D15), subjects should fast at least 8 hours (10 hours on fed dosing day for the optional Food Effect sub-study) before dose administration and 1 hour (4 hours on fed dosing day for the optional Food Effect sub-study)

after administration of PLX2853. On other PK sample collection days, subject should fast for 2 hours prior to their visit.

5.2.4 Effect of Food on PLX2853

In order to obtain more complete information on the PK profile of PLX2853, PK sampling will be performed in an optional Food Effect sub-study in the Phase 2a monotherapy cohort following a single dose of PLX2853 given 3 or 4 days prior to the start of continuous dosing. Food effect will be examined between test (fed state, Day -4 or -3) and reference (fasted state, Cycle 1 Day 1) treatments using a 1-way crossover design. On Day -4 or -3 following an overnight fast of at least 10 hours, subjects should start the recommended low-fat meal before administration of the drug product and complete the meal in 30 minutes or less. A single dose of PLX2853 should be taken with 8 ounces (240 mL) of water and within 30 minutes after the low-fat meal. No food is allowed for at least 4 hours after the dose.

The low-fat test meal should be approximately 400–500 calories, with approximated 25% of total caloric content coming from fats. An example low-fat test meal is 8 ounces of milk (1% fat), 1 boiled egg, and 1 packet flavored instant oatmeal made with water. A comparable meal may be substituted as long as it contains a similar amount of calories and % fat. The test meal, start and completion time of consumption of the meal, and the proportion consumed by the patient will be recorded on a case report form (CRF). On Day -4 or -3, PK samples will be collected at predose, 0.5, 1, 2, 3, and 5 hours postdose. Additional labs and safety assessments will be performed as specified in the Schedule of Events (Synopsis Table 1).

On C1D1 subjects should fast at least 8 hours before dose administration and 1 hour after dose administration. All labs and safety assessments specified on C1D1 in the Schedule of Events (Synopsis Table 1) must be completed on C1D1.

The Day -4 or -3 (test) and Day 1 (reference) exposures will be compared. The CI_{90} of the ratio of the test treatment (fed) relative to the reference treatment (fasted) will be obtained. No food effect will be confirmed if the CI_{90} falls between the 80% to 125% interval following the 2-sided test procedure.

5.3 Dose Escalation (Phase 1b PLX2853 + Carboplatin Only)

In Phase 1b (PLX2853 + carboplatin combination) dose escalation, cohorts will be enrolled using a standard “3+3” design. The starting dose level of PLX2853 will be 40 mg/day plus a target AUC of 5 mg•min/mL dose of carboplatin (Cohort 1). In the absence of a DLT in the first cycle of treatment and in conjunction with review of the PK and available PDx data from each cohort by the Study Committee, dose escalation is planned to occur in the following manner:

- DLTs will be assessed in the first treatment cycle (up to carboplatin dosing on Cycle 2 Day 1).

- The starting dose of PLX2853 will be 40 mg/day (Cohort 1), which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day.
- Carboplatin will be administered using a target AUC of 5 mg•min/mL on Day 1 of each 28-day treatment cycle per label. Carboplatin must be given within 7 days of Cycle 2 Day 1 (delays due to reasons other than toxicity will not be assessed as a DLT).
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be investigated. If that dose level is intolerable, Dose Level -2 (PLX2853 20 mg/day + carboplatin AUC 4 mg•min/mL) will be studied. If that dose level is intolerable, the study will be halted.
- In the absence of a DLT, a second cohort with a PLX2853 dose of 80 mg/day will be investigated (Cohort 2).

5.3.1 Dose Escalation Rules

Dose escalation will occur in accordance with the following rules:

- A minimum of 3 to 4 subjects will be initially enrolled in Cohort 1.
- If a DLT is observed in 1 subject in a given cohort, up to 6 subjects will be treated at that dose.
- If DLTs are observed in 2 or more of 6 subjects (or ≥33% of the cohort) at a dose level, the dose at which this occurs will be considered intolerable and the MTD will have been exceeded.
- The highest dose level at which 0 of 3 subjects or 0 or 1 of 6 subjects experience a DLT will be declared the RP2D. If 3 to 4 subjects were initially evaluated at that dose level, an additional 2 to 3 subjects may be enrolled to evaluate for DLTs at that dose level for confirmation. Up to 6 additional subjects with a known ARID1A mutation (unless otherwise approved by the Medical Monitor) may be treated at the RP2D at the discretion of the Sponsor for dose confirmation purposes.
- In order to be DLT evaluable a subject must not have missed more than 25% of study drug for reasons other than AE and must not have missed receiving carboplatin within 7 days of Cycle 2 Day 1 (if applicable) for reason other than AE. If a subject misses more than 25% of the doses for Cycle 1 (e.g., >7 doses of PLX2853 in 28 days) during the DLT window for reasons other than an AE, additional subject(s) may be enrolled to provide adequate data for dose escalation decision making. Subjects who do not complete Cycle 1 for reasons other than drug toxicity may be replaced. Subjects must receive their Cycle 2 Day 1 carboplatin dose to be considered evaluable unless the reason for missing carboplatin is due to an AE.

- Once all ongoing subjects in a dose cohort have been treated for at least 2 cycles and the safety and tolerability of that dose level has been established, intra-subject dose escalation to that dose level may be permitted for subjects enrolled at lower dose levels who have not experienced an unresolved Grade 3 or higher treatment-related toxicity and have completed 2 cycles. Any intra-subject dose escalation requires a discussion and agreement with the Medical Monitor.
- After dosing has been completed in each cohort, safety, PK, and PDx data (if available) will be reviewed, and dose escalation decisions will be made by the Study Committee. Dose escalation decisions will also take into consideration safety information beyond the DLT period from earlier cohorts.
- If no DLT is observed, the recommended dose for further evaluation may be established based on toxicity, PK, convenience of dosing, and PDx (if available) in subjects treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days.
- PLX2853 and carboplatin may not be dose escalated in the same cycle.

5.4 Concomitant Medications (and Procedures)

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. Other antineoplastic therapy for the treatment of the cancer for which subject is enrolled onto this study is not permitted (with the exception of certain standard of care hormonal therapies in consultation with the Medical Monitor). During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment or prophylaxis of an AE), the treatment must be recorded on the electronic case report form (eCRF), including the reason for treatment, generic name of the drug, dosage, route, and date of administration.

PLX2853 was stable in human liver S9 fractions with 1 metabolite (M1) detected. CYP2C8 and CYP3A4 are the major contributors for the formation of the PLX2853 oxidative metabolite M1. Their relative contributions to the formation of M1 were similar. However, because the rate of metabolism is very low, CYP2C8 and CYP3A4 inhibitors are not expected to have a significant effect on the clearance of PLX2853. Until information regarding exposure-toxicity and exposure-response relationships are available with PLX2853, concomitant CYP3A4 and CYP2C8 inhibitors and/or inducers should be avoided and may be administered after study entry with Medical Monitor approval, in the event they alter the systemic exposure to PLX2853 (see Appendix 2 for an example list of strong CYP3A4/2C8 inhibitors and inducers).

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, subjects should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines.

As per international guidance on antiemetic use in cancer subjects, generally, a single-agent antiemetic should be considered (NCCN 2020; Roila 2016).

Locally acting antacids may be used for initial presentation of gastroesophageal reflux disease (GERD). If locally acting antacids do not properly control GERD, proton pump inhibitors and other gastric pH modifiers may be used. All antacids, proton pump inhibitors, and other gastric pH modifiers should be administered 2 hours after PLX2853 administration.

The use of biotin (i.e., Vitamin B7) or supplements containing biotin higher than the daily adequate intake of 30 µg is prohibited during the study (NIH-ODS 2020). A total daily dose of 30 µg or less is allowed. Use of herbal, alternative, and food supplements (i.e., PC-Spes, Saw Palmetto, St. John's Wort, etc.) and probiotics must be discontinued before treatment start. Daily multi-vitamin (provided it does not contain biotin >30 µg/day), calcium, and Vitamin D are permitted.

Concomitant medications known to prolong the QT interval (see Appendix 4) are prohibited while receiving study drug (drugs with a low risk of QTc prolongation that are needed for infection control or nausea may be permitted with approval from the Medical Monitor).

All ongoing medications and therapies (including herbal products, nutritional supplements, and nontraditional medications) at Screening will be considered prior medications. All medications and procedures must be recorded on the appropriate eCRFs at the start of Screening until 30-day FU Visit procedures are performed or until the initiation of a non-protocol therapy for the underlying malignancy, whichever occurs first.

Palliative radiotherapy may be used for the treatment of pain at the site of bone metastases that were present at baseline following the completion of Cycle 1, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a subject undergoes therapeutic palliative radiation treatment and 7 days after completing radiation treatment. Study treatment should be restarted within 21 days as long as any bone marrow toxicity has recovered.

5.5 Precautions and Restrictions

There are no non-medication-related restrictions or precautions.

5.6 Management of Clinical Events

All necessary support care shall be available to subjects. For dose modification guidelines, see Section 6.2.

5.7 Blinding and Unblinding

Blinding methods will not be employed; PLX2853 and carboplatin (if applicable) will be administered in open-label fashion.

5.8 Preparation, Reconstitution, and Dispensation

PLX2853 is an anti-cancer drug and, as with other potential toxic compounds, caution should be exercised when handling PLX2853 (see Section 5.10). Specific instructions on preparation, reconstitution, and dispensation will be provided in the Study Pharmacy Manual.

Carboplatin will be prepared and administered per the label.

5.9 Packaging and Labeling

PLX2853 tablets are manufactured, packaged, and labeled according to Good Manufacturing Practice and Good Clinical Practice (GCP) at the following address:

BioDuro LLC (formerly Formex LLC)
11011 Torreyana Road #100
San Diego, CA 92121

Carboplatin is packaged per the label.

5.10 Storage, Handling, and Accountability

PLX2853 tablets should be stored at room temperature 20°C to 25°C (68°F–77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Subjects will be requested to store PLX2853 at the recommended storage conditions noted on the label. Carboplatin will be stored at the recommended storage conditions per the label.

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

All unused and partially used study drug must be sealed and returned to the Sponsor or designee or destroyed on site in accordance with the established procedures for drug destruction. Details of destruction, including, but not limited to, the number of boxes destroyed, batch number, and the date and method of destruction must be recorded on the study drug destruction logs.

5.11 Other Protocol-specified Materials

Central laboratory kits will be provided for sample collection, shipment, and storage for PK and PDx analyses.

6.0 DOSE-LIMITING TOXICITIES AND DOSE MODIFICATIONS

6.1 Definitions of Dose-limiting Toxicity

DLTs are defined as clinically significant AEs or laboratory abnormalities occurring during the first cycle of study drug administration that are *at least possibly related* to either PLX2853 or carboplatin and clearly unrelated to disease progression, concurrent illness, or concomitant medication, and that meet one of the following CTCAE v5.0 criteria below. DLTs will be evaluated for the monotherapy safety lead-in subjects as well as each Phase 1b (PLX2853 + carboplatin) escalation cohort. Toxicities occurring in treatment Cycle 2 or later will be reviewed and their impact on subsequent dosing levels and frequency assessed.

In Phase 1b (PLX2853 + carboplatin), there will be a 24-hour delay between the first and subsequent subjects enrolled in each dose escalation cohort to maximize the safety of enrolled subjects.

Subjects participating in the optional Food Effect sub-study as well as the monotherapy safety lead-in will be DLT evaluable from the date of first dose and the DLT window for these patients will be 28 days from C1D1.

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

DLTs are defined as follows:

- **Hematologic Toxicities**
  - Grade 4 neutropenia lasting >7 days
  - Grade ≥3 febrile neutropenia
  - Grade 4 thrombocytopenia
  - Grade ≥3 thrombocytopenia lasting >7 days or associated with clinically significant bleeding
  - Grade 4 anemia
- **Non-hematologic Toxicities**
  - Any dose reduction required during Cycle 1 due to an AE
  - Any treatment delay of >7 consecutive days during Cycle 1 due to study drug-related Grade ≥2 AEs that fail to resolve to baseline or Grade ≤1
  - Any case of Hy's law defined as AST or ALT >3 × ULN with concurrent total bilirubin >2 × ULN, absence of cholestasis (elevated alkaline phosphatase (ALP) >2 × ULN), and no alternative etiology which can explain the combination of increased AST or ALT and total bilirubin, such as viral hepatitis A through E, other preexisting or acute liver disease, or another drug capable of causing the observed injury

- Any Grade ≥3 increase in AST/ALT (only for subjects without hepatic metastasis and with baseline values within normal limits)
- AST/ALT >5 × ULN for ≥14 days or any AST/ALT >8 × ULN (only for subjects with hepatic metastasis or with abnormal baseline values)
- Grade 3 nausea, vomiting, or diarrhea that does not resolve to Grade ≤2 in ≤72 hours
- Any Grade 4 vomiting or diarrhea (life-threatening; urgent medical intervention indicated) irrespective of duration
- Any non-clinically significant Grade 3 or higher electrolyte imbalance that does not correct to Grade ≤1 in ≤5 days
- Any Grade 3 or Grade 4 clinically significant electrolyte imbalance (life-threatening; urgent medical intervention indicated) irrespective of duration
- Unless specifically noted in other DLT criteria any Grade ≥3 (AE or laboratory abnormality) toxicity that does not resolve to Grade ≤2 within 7 days despite maximal medical intervention, except for the following:
  - Grade 3 neuropathy in subjects with pre-existing Grade 2 neuropathy
- Any other Grade ≥3 toxicity (except those noted above) for which either the Principal Investigator or Sponsor deems further dose escalation inappropriate
- Carboplatin Cycle 2 Day 1 dose reduction (AUC not total dose) or carboplatin Cycle 2 Day 1 dose interruption for >7 days
  - An allergic reaction to carboplatin or any AEs associated with the allergic reaction during Cycle 1 will not be considered a DLT. The subject will be noted as inevaluable and will be replaced.
- Any death not clearly due to underlying disease or an extraneous cause

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

AEs occurring in treatment Cycle 2 or later will be collected, analyzed, and discussed with the Study Committee to help inform the selection of doses for subsequent study cohorts, including the option of dose reduction. If cumulative toxicities are observed requiring dose reductions in 1 of 3 or more subjects, dose escalation may be halted and more subjects may be treated at that or a lower dose level.

6.2 Dose Modification Guidelines

Reduction of dosing may take place for study drug-related AEs in Cycle 2 and beyond for subjects enrolled in the Phase 1b PLX2853 + carboplatin dose escalation cohorts or the safety

lead-in for the Phase 2a PLX2853 monotherapy part and at any time for subjects enrolled in the Phase 2a PLX2853 + carboplatin dose expansion cohorts and for subjects that are not part of the safety lead-in of the Phase 2a PLX2853 monotherapy part. Table 7 presents guidelines for dosage modification and re-treatment for PLX2853-related toxicities. These parameters are only a guide and are not intended to supersede the clinical judgment of the treating physician. Dose modifications of carboplatin should follow the label, as well as the guidance below.

If an allergic reaction to carboplatin occurs after Cycle 1, both PLX2853 and carboplatin should be held until a carboplatin desensitization protocol is conducted per institutional standard of care. Dosing of study drugs may resume after the subject's successful completion of a desensitization protocol and with approval from the Medical Monitor.

For the combination parts of the study, if 1 study drug needs to be held due to an AE, then both drugs need to be held until the AE resolves per the dose modification guidelines unless Medical Monitor approval is granted. If 1 study drug needs to be permanently discontinued, then both study drugs must be permanently discontinued and the subject taken off study unless approval granted by the Medical Monitor.

The dose modification/reduction guidelines are for clinically significant toxicities that are at least possibly related to PLX2853 administration. Definitions of "clinically significant" and "related" will be made based on the judgment of the Investigator, and the case should be discussed with the Medical Monitor as needed. All adjustments should be made in consultation with the Medical Monitor.

If there is a PLX2853 dosing hold within a cycle (e.g., due to toxicity), study drug dosing will resume on the next appropriate day. For example, if the subject has a study drug hold for 10 days beginning on Cycle 2 Day 8 (Day 1 of hold), the subject should resume the schedule of events for Cycle 2 Day 18. If study assessments are missed during a hold, those assessments will be noted as not done and the next scheduled assessment day procedures will be followed. If the drug hold is less than 3 weeks between cycles, the first day of dosing in subsequent cycles should be considered Day 1, and all procedures calculated based on that starting day. For example, if the subject has a study drug hold on Cycle 2 Day 15 for 15 days, the subject will resume the schedule of events for Cycle 3 Day 1. Every attempt should be made to keep to the 28-day cycle.

In Cycle 2 and beyond, dose interruptions for Grade ≤2 non-hematologic toxicity can be implemented for up to 1 week at the discretion of the treating physician to manage clinically significant toxicities. No dose reduction is required when resuming treatment.

Dosing interruptions longer than 2 weeks should generally result in discontinuation from the study, unless the subject has demonstrated a clinical benefit from therapy and would like to continue dosing with study drug after discussion with the Sponsor and approval by the Medical Monitor.

Table 7: Recommended PLX2853 Dose Modifications

PLX2853-Related Toxicities	Frequency	When to Hold or Stop	Dose Adjustments for Resumption[a]
Grade 3 or 4 neutropenia	1st Appearance	Interrupt until ANC recovers to ≥1.5 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1.5 × 10^9/L in ≤7 days, resume at same dose.
			If not recovered to ANC ≥1.5 × 10^9/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until ANC recovers to ≥1.5 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1.5 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1.5 × 10^9/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	Discontinue permanently; growth factor support permitted	N/A
Grade 3 or 4 febrile neutropenia	1st Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC ≥1.5 × 10^9/L and T ≤38°C in ≤7days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1.5 × 10^9/L after 7 days, discontinue permanently.
	2nd Appearance	Discontinue permanently; provide growth factor support	N/A
Grade 3 or 4 thrombocytopenia without bleeding	1st Appearance of G3	Interrupt until PLT ≥75 × 10^9/L	If recovered to PLT ≥75 × 10^9/L ≤7 days, resume at same dose.
			If not recovered to PLT ≥75 × 10^9/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance of G3 or 1st Appearance of G4	Interrupt until PLT ≥75 × 10^9/L	If recovered to PLT ≥75 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to PLT ≥75 × 10^9/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance of G3 or 2nd Appearance of G4	Discontinue permanently	N/A

PLX2853-Related Toxicities	Frequency	When to Hold or Stop	Dose Adjustments for Resumption[a]
Grade 3 or 4 thrombocytopenia with clinically significant bleeding	1st Appearance	Discontinue permanently	N/A
Other Grade 3 toxicities (excluding transaminase increases)	1st Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered ≤5 days, resume at same dose.
			If symptoms persist for >5 days despite supportive management, reduce by 1 dose level.
	2nd Appearance	Interrupt until resolved (Grade 0–1); start symptomatic treatment if possible	If recovered ≤5 days, reduce dose by 1 dose level.
			If symptoms persist for >5 days despite supportive management, discontinue permanently.
	3rd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Grade 3 non-hematologic toxicities	1st Appearance	Interrupt until resolved to Grade ≤1 or baseline	If recovered to Grade ≤1 or baseline in ≤14 days, restart at a reduced dose by 1 dose level.
			If symptoms persist at Grade ≥2 for >14 days, discontinue permanently.
Grade 4 non-hematologic toxicities	1st Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A

PLX2853-Related Toxicities	Frequency	When to Hold or Stop	Dose Adjustments for Resumption[a]
Transaminase increases	• ALT or AST >8 × ULN but <20 × ULN • ALT or AST >5 × ULN for more than 2 weeks • ALT or AST >3 × ULN and total bilirubin >2 × ULN or INR >1.5 (in absence of anticoagulation) • ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Immediately hold dose and discuss with Medical Monitor. Institute close monitoring. Any decision to restart after transaminases return to baseline must be discussed with the Medical Monitor.	If clinically indicated, restart at a reduced dose.
	• Hy's Law: AST/ALT >3 × ULN and total bilirubin >2 × ULN and ALP <2 × ULN with no alternative etiology for the observed injury • ALT or AST >20 × ULN	Discontinue permanently	N/A
QTcF >500 msec or 60 msec increase from baseline verified on repeat ECG	1st Appearance	Interrupt study drug until resolved.	Upon recovery to QTc ≤500 msec (Grade ≤2), restart at a reduced dose. Permanently discontinue study drug if the QTc 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).[b]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECG = electrocardiogram; G = grade; INR = International Normalized Ratio; N/A = not applicable; PLT = platelet; QTcF = AT interval corrected using Fridericia's equation; T = temperature; ULN = upper limit of normal

[a] See Table 6 for dose levels.

[b] QTc: Only 1 dose reduction is permitted per subject. Prior to and following treatment initiation or after dose modification of study drugs for QTc prolongation, evaluate ECG and electrolytes (including potassium, magnesium, and calcium) after 15 days, and monthly thereafter or more often as clinically indicated.

7.0 STUDY CONDUCT AND ASSESSMENTS

7.1 Study Conduct

7.1.1 Study Personnel and Organizations

The contact information for the Medical Monitor for this study is presented in Table 8. The contact information for the central and any additional clinical laboratories, the coordinating investigator for each member state/country, and contract research organization (CRO) can be found in the Study Reference Manual. A full list of investigators is available in the Sponsor's investigator database.

Table 8: Contact Information

Medical Monitor: (Emergency Contacts)	Athanasios Tsiatis, MD Vice President, Clinical Development Plexxikon Inc. 329 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: +1-510-647-4142 +1-510-590-6443 (after business hours) Fax: +1-510-548-8014 E-mail: atsiatis@plexxikon.com
SAE Reporting Contact	Report all SAEs, whether related or not to study drug, by emailing a completed SAE form within 1 working day of receiving knowledge of the event to: Email: Plexxikon.Safety@premier-research.com Fax: +1-215-972-8765

SAE = serious adverse event

7.1.2 Study Committee

The Study Committee will include at minimum the Sponsor Medical Monitor and participating Principal Investigators. The Study Committee will meet for Phase 1b PLX2853 + carboplatin dose escalation decisions and approximately monthly during the Phase 2a PLX2853 monotherapy and Phase 2a PLX2853 + carboplatin dose expansion portions of the study. Data to be evaluated may include (but are not limited to): deaths, SAEs, AEs (including treatment-related AEs), reasons for treatment discontinuation or dose modification/ interruption, trends in laboratory evaluations, PK, and efficacy. The Study Committee may also review any biomarker data if it becomes available.

7.1.3 Arrangements for Recruitment of Subjects

Recruitment and enrollment strategies for this study may include recruitment from the Investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC).

7.1.4 Treatment Group Assignments

This is an open-label, parallel, 2-part study: a Phase 2a PLX2853 monotherapy part in subjects with advanced gynecological malignancies with a known ARID1A mutation and a Phase 1b/2a PLX2853 + carboplatin dose escalation/dose expansion part in subjects with platinum-resistant EOC. In the Phase 2a PLX2853 monotherapy part, subjects will receive PLX2853 80 mg/day. In parallel, the initial dose level of PLX2853 in the Phase 1b combination dose escalation will be 40 mg/day. Thereafter, dose escalation (including alternative dosing schedules) will proceed as described in Section 5.3.

Subjects with a known ARID1A mutation must be enrolled to the Phase 2a PLX2853 monotherapy cohort unless approved by the Medical Monitor. Once enrollment to this cohort is complete, subjects with a known ARID1A mutation may be considered for enrollment to the Phase 1b/2a PLX2853 + carboplatin cohorts.

7.1.5 Withdrawal of Subjects from Drug Treatment and Study; Subject Replacement

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

The reasons a subject may discontinue or be withdrawn from the study include, but are not limited to: AE, clinically significant disease progression, subject request, investigator decision, protocol violation, subject noncompliance, and study termination by the Sponsor or IRB/IEC. When a subject discontinues or is withdrawn, the Investigator will notify the Sponsor and should perform the procedures indicated in the 30-day FU Visit column in the Schedule of Events approximately 30 days after discontinuation of study drug or prior to initiation of any new anti-cancer therapy, whichever occurs first. Follow-up information may be obtained for subjects who discontinue treatment in the study.

Subjects who discontinue PLX2853 treatment, or miss more than 25% of their expected doses, for reasons other than toxicity or clinically significant disease progression (e.g., protocol violation or noncompliance) during Cycle 1 may be replaced at the discretion of the Medical Monitor. Subjects in the Phase 1b/2a PLX2853 + carboplatin cohorts who miss carboplatin dosing on Cycle 1 Day 1 or Cycle 2 Day 1 for reasons other than toxicity will be replaced. Study drug administration may be discontinued for an AE or at the discretion of the Investigator.

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

7.1.6 Study Compliance

The study drugs PLX2853 and carboplatin (if applicable) will be provided only to eligible subjects under the supervision of the Investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Any discrepancy regarding the dose administered and the reason for the discrepancy will be recorded in the eCRF. At each clinic visit, subjects will be questioned about their compliance with study drug administration, and their dosing diary should be reviewed.

7.1.7 Enrollment of Subjects

After potential subjects have been identified by the site personnel, the site will inform the Sponsor/Sponsor's representative and a slot may be temporarily reserved for the subject. Once informed consent has been obtained and all Screening assessments are completed, the site personnel will email the Sponsor/Sponsor's representative with the enrollment packet. The Sponsor's Medical Monitor or designee will review and approve the enrollment (via email typically), inform the Investigator that the subject has been approved for enrollment, and assign the appropriate dose level. A subject will be considered enrolled once they have received their first dose of PLX2853. Subjects must continue to meet all eligibility criteria that are repeated at the time of initiation of C1D1 dosing, except for optional Food Effect subjects who are required to meet all eligibility criteria before dosing on D-4 or D-3.

Subjects who are approved to enroll (signed enrollment form returned by Plexxikon) but do not receive study drug will be considered screen fails.

Further information may be found in the Study Reference Manual.

7.1.8 Protocol Deviations

A protocol deviation is any departure from the protocol. Significant protocol deviations are defined as departures from protocol-required processes or procedures that affect subject safety or potential benefit or confound assessments of safety or clinical activity. Protocol deviations may be grouped into the following categories:

- Enrollment criteria
- Study activities (e.g., missed evaluations or visits, data verification issues)
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay, or discontinuation criteria
- Use of a prohibited medication

- AE not reported/SAE reported late
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

Significant protocol deviations should be reported to the Sponsor immediately upon awareness and submitted to the site's IRB/IEC per institutional policy.

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

Screening procedures are to be performed within 28 days of Cycle 1 Day 1 unless otherwise specified in the Schedule of Events (Synopsis Table 1, Synopsis Table 2, Synopsis Table 3).

The 30-day FU Visit will take place approximately 30 days after last dose of PLX2853 or prior to starting any new anti-cancer therapy, whichever occurs first (see Section 7.1.5 for reasons for discontinuation or withdrawal of a subject from the study).

Survival follow-up can be via clinic visit, phone call to the subject or referring physician, or other method deemed appropriate by the site and should assess survival, progression, subsequent therapy, and response. Subjects will be followed until death, withdrawal of consent, or loss to follow-up according to the following schedule:

- First 2 years after the 30-day FU Visit – Every 3 months
- Third year after the 30-day FU Visit and beyond – Every 6 months

Any subject with a confirmed response who discontinues treatment for reasons other than disease progression will continue to be followed per standard of care and no less than every 3 months until documented disease progression, initiation of a new anti-cancer treatment, or 1 year from discontinuation of study treatment. Radiographic scan data will be collected and if scan data are not available, a scan will be obtained every 3 months until 6 months of radiographic follow-up after confirmed response has been obtained. Refer to the Schedule of Events (Synopsis Table 1, Synopsis Table 2, Synopsis Table 3).

7.1.9 Disease Assessment

Response will be assessed by the Investigator with RECIST v1.1 using imaging appropriate for the disease. The same radiographic procedure used to assess disease sites at Screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessment of tumor burden will occur every 2 cycles or more frequently as clinically indicated. Redacted copies of pathology, molecular pathology, photography (if applicable) and radiology reports should be sent

to the Sponsor as part of the enrollment packet and after each tumor response assessment. In addition, redacted copies of radiology scans should be available for an independent review if requested by the Sponsor.

See Appendix 3 for details of RECIST v1.1.

Subjects without clinically significant radiographic disease progression who are receiving clinical benefit may continue on treatment with Medical Monitor approval.

7.1.9.1 Fresh Tumor Biopsy

Archival tissue samples will be collected at Screening. All subjects will be required to permit exploratory evaluations of their archival tumor tissue whenever archival tissue is available. If >6 months (approximately) have elapsed since the last biopsy, a repeat biopsy(ies) of representative lesions (in the judgment of the Investigator) is recommended. Subjects with biopsy-accessible tumors may be asked to participate in exploratory evaluations of paired biopsies with samples taken at Screening, Cycle 2 Day 1, and any other time per the discretion of the Investigator (mandatory for subjects in Phase 2a cohorts, optional for subjects in Phase 1b cohorts). If the archival tissue provided was collected within 2 months of Screening, a fresh sample does not need to be collected at Screening. The biopsies should be from the same lesion if possible/feasible, and preferably from a non-target lesion.

Further handling/shipping instructions may be found in the Laboratory Manual.

7.1.10 Pharmacokinetic and Pharmacodynamic Assessments

All blood, urine, and tissue samples may be used interchangeably and for multiple types of biomarker and PK assays. Because the identification of new biomarkers of disease and treatment response is a rapidly developing field, a definitive list of assays remains to be determined. Subjects should be instructed not to take their PLX2853 dose at home on PK or PDx collection days.

In addition to scheduled PK assessments, samples for PK should be collected for any dose modification at the time points specified in the Schedule of Events (Synopsis Table 1, Synopsis Table 2, Synopsis Table 3) within 2 weeks of the modification or at the next scheduled clinic visit, whichever occurs closest to the new dosing regimen. Additional samples for PK may also be collected if a subject experiences a DLT, SAE, or AE of special interest (AESI). A list of protocol-required PK and PDx assessments is provided in Appendix 1.

A total volume of blood collected in Cycle 1 (28-day cycle) will be approximately 261.5 to 375 mL and all subsequent cycles will be no more than approximately 76 to112 mL. Further information may be found in the Laboratory Manual.

PK draws should be taken from the opposite arm (not the arm with the IV catheter) whenever possible and when not possible from a site below (distal to) the IV site.

7.1.10.1 Pharmacokinetic Assessments

PLX2853 PK data will be analyzed in each dosing cohort for C_{max}, AUC, and accumulation ratio at steady state and compared with prior dose levels. The number of subjects at a given dose level may be increased as a result of the review of safety, observed or anticipated disease activity, and PK data. Additional dosing schedules may be studied, such as alternate day dosing (e.g., every other day) depending on emerging safety and PK data.

In addition, PK analysis may include analysis of PLX2853 metabolites.

7.1.10.2 Biomarker Samples and Pharmacogenomics

Baseline subject blood samples (serum, plasma, whole blood) will be obtained for PDx and biomarker assessments. These may be repeated at subsequent time points throughout the study. In addition, subjects will be asked to submit archival tumor samples, and may be asked to have subsequent tumor biopsies while on the study (optional for subjects in Phase 1b cohort and mandatory for subjects in Phase 2a cohorts). These tumor samples may be used for PDx and biomarker assessments. While some of the assessments are prospectively described in the protocol, new assessment methods may emerge during the study or after it has concluded. Hence some samples may be stored and analyzed at a later date as newer technologies emerge.

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

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

- Genetic analyses (sequencing) of tumor tissues for mutations relevant to bromodomain inhibition
- Histochemical and/or protein analysis of tumor, plasma tissue, peripheral blood cells for changes relevant to bromodomain inhibition
- Genomic analysis and expression arrays may also be performed for exploratory purposes
- RNA sequencing
- Serum protein and cytokine analysis
- Analysis of HRD status

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

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

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

For subjects who participate in pharmacogenetic testing, a blood sample should be collected at the Screening Visit or as indicated in the Schedule of Events. This sample may be analyzed only for genes suspected to contribute to the safety and efficacy of the study medications. The analysis may also include a comprehensive evaluation of genetic information, with a particular focus on specific genetic changes considered to potentially predict responsiveness or resistance to treatment.

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

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

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

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

Sample collection, preparation, handling, storage, and shipping instructions are in the Laboratory Manual. Blood volume for blood draws is provided in Section 7.1.11.7.1.

7.1.11 Safety Assessments

Safety and tolerability will be monitored and determined by reported AEs (including deaths, other SAEs, and TEAEs), laboratory tests (hematology, clinical chemistry, coagulation, serum inflammation marker, and urinalysis), ECG, physical exams (including weight), and vital signs.

7.1.11.1 Medical and Medication History

Medical history includes clinically significant diseases, surgeries, cancer history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the subject within 28 days prior to the Screening Visit and history of treatment for the primary diagnosis, including prior systemic, radiation treatment, and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the Investigator.

7.1.11.2 ECOG Performance Status Assessment

An assessment of performance status will be performed using the ECOG Performance Status scale of 0 to 5 (Appendix 5).

7.1.11.3 Physical Examinations

The Investigator or qualified designee will conduct physical examinations. A complete physical examination will be conducted at Screening and 30-day FU Visit, and a symptom-directed physical examination (based on interval history and/or AEs) will be conducted at all other visits.

7.1.11.4 Vital Signs

Vital signs will be recorded and will include measurements of body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure. Predose vital signs must be obtained on days that PK/PDx samples are taken. On non-PK/non-PDx days, vital signs do not need to be predose and subjects may self-administer PLX2853 at home either prior to or after their clinic visit (if applicable).

7.1.11.5 Height and Weight

Height (Screening only) in centimeters and body weight in kilograms will be measured.

7.1.11.6 Electrocardiogram

Subjects should rest in the supine or semi-recumbent position for at least 5 minutes before 12-lead ECG recording is started. The ECGs should be reviewed, signed, and dated by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. The results will include heart rate, PR interval, QRS interval, QT interval, and QTcF interval with QTcF calculation. Fridericia's correction is required: $QTcF = (QT)/3\sqrt{(RR)}$.

Triplicate ECGs should be done at Screening and predose Cycle 1 Day 1 (approximately 10 seconds per ECG over a 5 minute period). All other ECGs are single tracings. Additional ECGs should be obtained to evaluate AEs as applicable per standard of care.

7.1.11.7 Safety Laboratory Assessments

The Investigator will monitor the safety laboratory test findings. If any laboratory test is abnormal during the course of the study, it will be followed at the discretion of the Investigator. Abnormalities of laboratory tests will be evaluated by the Investigator and assessed as either clinically significant or not clinically significant. Abnormal laboratory values deemed by the Investigator to be clinically significant and, thus, constitute or are associated with an AE, must be reported on the AE form. Abnormal laboratory values that require intervention must be reported on the Adverse Event form whether or not deemed clinically significant.

A complete list of required safety laboratory tests is provided in Appendix 1. Additional details for specific tests are provided in the Laboratory Manual.

7.1.11.7.1 Blood Collection

The estimated volumes of blood to be collected at each visit of the study are shown in Table 9. The quantities of blood are within accepted limits of 10.5 mL/kg or 550 mL (whichever is smaller) per National Institutes of Health and other published guidelines (DF/HCC 2012; NIHCC 2009; NS LIJ 2013).

Table 9: Approximate Blood Sample Volumes Collected

	Blood Sample Volumes (mL)										
	SCR	C1					C2		C3–4	C5+	
STUDY DAY►	D-28 to D-1	D-4 or D-3	D1	D8	D15	D22	D1	D15	D1	D1	30-day FU
WINDOW (days)►				± 2	± 2	± 2	+ 3	± 3	± 5	± 5	± 7
TEST▼											
PG blood sample	6										
Hematology[a]	8	8	8	8	8	8	8	8	8	8	8
Chemistry[a]	8	8	8	8	8	8	8	8	8	8	8
Coagulation tests[a]	8	8	8	8	8	8	8	8	8	8	8
C-reactive protein[a]	0-5	5	5	5	5	5	5		5	5	5
Tumor markers[a]	0-10	10	10				10		10	10	10
Hepatitis A/B/C and HIV tests	9										
PDx blood samples		38.5	38.5		25		31		31	31	31
PK blood samples		36	36		36		18		18	6–18	6
TOTAL VOLUME[b]	**39-54**	**113.5**	**113.5**	**29**	**90**	**29**	**88**	**24**	**88**	**76–88**	**76**

30-day FU = 30-day follow-up visit; C = cycle; D = day; PDx= pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetic; SCR = Screening

[a] Estimated volume. Actual volume will be per site's standard of care.

[b] The total blood volume drawn over Cycle 1 is approximately 261.5 to 375 mL and in subsequent cycles is approximately 76 to 112 mL.

7.1.12 Pregnancy Testing

All women of child bearing potential who are being considered for participation in the study will be tested for pregnancy with a serum β-human chorionic gonadotropin test within 7 days prior to taking the first dose of study drug. Additional pregnancy testing should be scheduled per local regulations where applicable. A serum or urine pregnancy test will be completed at the 30-day FU Visit.

8.0 STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Randomization and Stratification

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

8.2 Definitions and Populations for Analysis

A screened subject is defined as a subject who signed an informed consent form.

An enrolled subject is defined as a subject who has received at least 1 dose of study drug.

A screening failure (screen failure) is defined as a subject who signs consent but is not dosed.

8.2.1 Evaluable Populations

The Efficacy Evaluable Population consists of all subjects who received any treatment with PLX2853 and who have at least 1 post-baseline target lesion response assessment or discontinued because of clinical progression or drug-related toxicity. The Safety Population consists of all subjects who receive any treatment with study drug and have any follow-up data.

8.3 Procedures for Handling Missing, Unused, and Spurious Data

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

8.4 General Methodology

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

8.5 Baseline Comparisons

Demographic and baseline characteristics will be summarized by cohort. The last assessment performed prior to the first PLX2853 dose will be considered baseline.

8.6 Efficacy Analysis

8.6.1 Phase 1b (Dose Escalation) (PLX2853 + Carboplatin)

Data will be tabulated and evaluated by descriptive statistics. Statistical analyses for the primary objectives will be descriptive only, with no hypothesis testing. Summary tables will present results for each dose cohort. Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables.

Response to treatment will be evaluated using investigator-determined RECIST v1.1 criteria (Appendix 3).

8.6.2 Phase 2a (PLX2853 Monotherapy) and Phase 2a (PLX2853 + Carboplatin Combination)

8.6.2.1 Primary Efficacy Analysis

The primary objectives of the Phase 2a cohorts of the study are to determine the antitumor activity (ORR) of PLX2853 monotherapy or PLX2853 + carboplatin combination. Response to treatment will be evaluated using investigator-determined RECIST v1.1 criteria (Appendix 3), with a minimum interval for confirmation of CR and PR of 4 weeks. Each Phase 2a cohort will enroll up to 26 evaluable subjects using a Simon's 2-stage design in which initially 12 evaluable subjects are enrolled. In the monotherapy cohort, the safety lead in of 6 subjects dosed at the level selected for Phase 2a will be included in the group of 12 evaluable subjects for stage 1. If ≥33% DLTs are seen during the initial safety lead in, the Safety Committee will convene to consider a dose reduction. If a dose reduction is deemed appropriate, the subjects in the initial safety lead in will need to be replaced and a repeat 6 subject safety lead in will need to be conducted at this lower dose. If 2 or more responses are observed in 12 evaluable subjects, another 14 evaluable subjects will be enrolled for a total of 26 subjects to that cohort. If 6 or more responses are observed, the study has 80% power with alpha of 0.05 to reject the ORR of 10% in favor of the ORR of 30%. Recruitment will stop within a cohort if no more than 1 response is observed after the initial 12 evaluable subjects have been accrued. ORR will be summarized per cohort along with their 95% confidence intervals (CIs). A 2-sided 95% CI will be calculated for the true response rate based on the Clopper-Pearson method.

8.6.2.2 Secondary Efficacy Analyses

A 2-sided 95% CI will be calculated for the true response rate based on the Clopper-Pearson method for secondary analyses.

Secondary efficacy analyses include the following:

- DCR: The percentage of subjects with confirmed CR, PR, or SD per RECIST criteria
- PFS: The number of days from the first day of PLX2853 treatment (Cycle 1 Day 1) to the date of the first documented disease progression or date of death from any cause, whichever occurs first. The time-to-event secondary efficacy endpoint of PFS will be summarized for each cohort using the Kaplan-Meier method. Subjects lost to follow-up or event-free as of the data analysis cutoff date will be right-censored.
- DOR: The number of days from the date of first response (PR or CR confirmed at least 28 days later) to the date of the first documented disease progression or date of death from any cause, whichever occurs first.

- OS: The number of days from the first day of PLX2853 treatment (Cycle 1 Day 1) to the date of death from any cause. The time-to-event secondary efficacy endpoint of OS will be summarized for each cohort using the Kaplan-Meier method. Subjects lost to follow-up or event-free as of the data analysis cutoff date will be right-censored.

8.7 Pharmacokinetics, Pharmacodynamics, Biomarkers

8.7.1 Pharmacokinetic Analysis

The PK parameters of PLX2853 will be assessed by measuring AUC from time zero to time of last observed concentration hours postdose ($AUC_{0\text{-last}}$), $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, $T_{1/2}$, and accumulation ratio at steady state.

Dose proportionality following study dosing will be explored by analyzing natural log-transformed PK variables, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate.

8.7.2 Pharmacodynamic and Other Biomarker Analysis

Planned biomarker analyses for PDx include, but are not limited to:

- Gene expression, nucleic acid sequencing, histochemical and/or protein analyses of plasma, peripheral blood cells, and/or tumor tissue
- Analysis of HRD status

Exploratory analysis of biomarker samples may also be performed to learn about the drug and disease properties.

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

8.8 Safety Analysis

Safety variables to be assessed will include assessment of AEs, physical examinations (including weight), laboratory test results (hematology, clinical chemistry, coagulation, serum inflammation marker, and urinalysis), ECG, and vital sign measurements.

AE terms recorded on the eCRFs will be mapped to preferred terms using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 23 or later. All TEAEs will be summarized according to the system organ class and preferred term within the organ class. TEAEs will be tallied for overall frequency (number and percentage of subjects), worst reported severity, and relationship to study drug for each preferred term per subject. SAEs will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

Laboratory variables will be examined using mean change in value from baseline to scheduled time points. Laboratory values will also be categorized according to their CTCAE v5.0 toxicity grade and tabulated by worst on-study toxicity grade. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first PLX2853 dose.

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

8.9 Interim Analysis

No formal interim analysis is planned.

9.0 ASSESSMENT OF SAFETY AND ADVERSE EVENTS

Safety and tolerability will be monitored and determined by serial physical examinations (including weight), vital signs, hematology and chemistry laboratory studies (including coagulation, serum inflammation marker, and urinalysis), ECGs, and reported AEs (including deaths and other SAEs and TEAEs). The Investigator will monitor the laboratory test findings. If any laboratory test is abnormal during the course of the study, it will be followed at the discretion of the Investigator. Abnormalities of laboratory tests are evaluated by the Investigator and assessed as either clinically significant or not clinically significant. Abnormal laboratory values deemed by the Investigator to be clinically significant and, thus, constitute or are associated with an AE, must be reported on the AE form. Abnormal laboratory values that require intervention must be reported on the AE form whether or not deemed clinically significant.

9.1 Definitions

9.1.1 Adverse Event Definition

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

- Any clinically significant worsening of a preexisting condition except for events clearly consistent with progression of disease under study as described in Section 9.3.2
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a study drug
- An AE that has been associated with the discontinuation of the use of a study drug

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting 1 or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

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

AEs will be graded in severity according to CTCAE v5.0 criteria.

9.1.2 Serious Adverse Event Definition

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

- Results in death
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires in-subject hospitalization longer than 24 hours or prolongation of existing hospitalization (see clarification in the paragraph below on planned hospitalizations). An emergency room visit without hospitalization is not considered a hospitalization.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse.

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

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

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the CRF. Any clinically relevant deterioration in

laboratory assessments or other clinical finding is considered an AE and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs, as defined in Section 9.1.2, that occur during the course of the study as defined in Section 9.3 must be reported within 1 working day of awareness by using the SAE Report Form. All SAEs and deaths must be reported whether or not considered causally related to the study drug, except for events clearly consistent with progression of disease under study as described in Section 9.3.2. SAEs and deaths will be reported by completing the SAE Report Form and by emailing (fax as back-up) the completed SAE Report Form to the designated recipient (Section 7.1.1). A sample of the SAE Report Form may be found in the Study Reference Manual. Follow-up information on the SAE may be requested by Plexxikon. SAEs reported to Product Safety must match the data provided on the eCRF. Contact information will be listed on the SAE Report Form.

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

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

Intensity for each AE, including any laboratory abnormality, will be determined by using the NCI CTCAE v5.0, as a guideline, wherever possible. The criteria are provided in the Study Reference Manual. In those cases where the NCI CTCAE criteria do not apply, intensity should be defined according to the following criteria:

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

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

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

In addition, the relationship may be confirmed by improvement on stopping the study treatment and reappearance of the event on repeated exposure.

9.3 Timing of Evaluation of Adverse Events and Serious Adverse Events

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

All SAEs will be recorded from the time the informed consent is signed through 30 days after last dose of study or prior to starting any new anti-cancer therapy, whichever occurs first. Any SAE occurring from time of consent to initiation of study drug that is related to a protocol-mandated procedure must be reported to Plexxikon or its designee within 1 working day of the knowledge of the event. All SAEs occurring from start of study drug through 30 days after administration of the last dose of study drug or prior to the administration of any new anti-cancer therapy, whichever occurs first, must be reported to Plexxikon or its designee within 1 working day of the knowledge of the event.

9.3.1 Adverse Events of Special Interest

At present, there are no AESIs identified for this study.

9.3.2 Worsening of Cancer

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

9.3.3 Overdose

Certain information, although not considered an AE, must be recorded in the eCRF and followed up as indicated for an AE. This may include the following:

- Overdose
  - Study drug overdose is the accidental or intentional use of PLX2853 in an amount at least 40% higher than the dose being studied or carboplatin in any amount above the target AUC dose. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF.
  - All AEs associated with an overdose or incorrect administration of study drug should be recorded on the adverse event CRF. If the AE also fulfills serious criteria, it should be reported as an SAE using the SAE Report Form.

9.4 Monitoring of Adverse Events and Period of Observation

AEs, both serious and non-serious, and deaths will be recorded on the CRFs up to and including the last visit at approximately 30 days after administration of the last dose of study drug or prior to the administration of any new anti-cancer therapy, whichever occurs first.

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

All SAEs must be followed by the Investigator until one of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to etiology other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

9.5 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study or up to 90 days (for subjects in the US) or 6 months (for subjects in Canada) after completing study treatment, she must inform her treating physician immediately and, if applicable, and permanently discontinue study drug. The Sponsor must also be contacted immediately by emailing or faxing a completed Pregnancy Form to Plexxikon or designee as described in the Study Reference Manual. The pregnancy must be followed through final outcome (i.e., beyond delivery) for SAEs.

10.0 ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

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

10.2 Data Quality Assurance

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

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

10.3 Electronic Case Report Form Completion

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

eCRFs will be completed for each study subject. Screen failure information will not be collected in the eCRFs. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF.

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

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

Plexxikon or a CRO designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the Investigator's study file.

10.4 Study Monitoring

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

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

10.5 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The study must fully adhere to the principles outlined in *Guideline for Good Clinical Practice E6 (R2), November 2016*, or with local law if it affords greater protection for the subject. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator or the Sponsor, as allowable by local regulations.

10.6 Subject Information and Informed Consent

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

10.7 Subject Confidentiality

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

10.8 Investigator Compliance

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

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

10.9 On-site Audits

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

10.10 Investigator and Site Responsibility for Drug Accountability

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

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

10.11 Product Complaints

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

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

10.12 Closure of the Study

The Sponsor currently has no plans to provide PLX2853 to study subjects after the close of the study or earlier subject withdrawal. However, the Sponsor will evaluate the appropriateness of continuing to provide PLX2853 to study subjects after evaluating study data pertaining to the primary efficacy outcome measure and safety. These analyses may be conducted prior to study completion. For subjects who are demonstrating a clinical benefit at the end of this study, the possibility of continuing their treatment in this or a roll-over protocol may be considered. Within 90 days of study closure, the Sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

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

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

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

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

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

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

10.13 Record Retention

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

10.14 Publication and Use of Information

All information regarding PLX2853 supplied by Plexxikon to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Plexxikon. It is understood that there is an obligation to provide Plexxikon with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of PLX2853 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

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

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APPENDIX 1: LABORATORY TESTS

Hematology

- Complete blood count with differential (absolute)
- Platelet count

Chemistry

- Sodium
- Potassium
- Chloride
- CO_2
- Calcium
- Phosphorus
- Magnesium
- Glucose
- Blood urea nitrogen
- Creatinine[a]
- Uric acid
- Albumin
- Total protein
- Total bilirubin
- Direct bilirubin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (AP)
- Lactate dehydrogenase (LDH)
- Gamma-glutamyl transferase (GGT)

[a] eGFR calculated using the following formula (CKD-EPI 2009):

$$eGFR = 141 \times \min(S_{Cr}/K, 1)^{\alpha} \times \max(S_{Cr}/K, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \times 1.159 \text{ [if Black]}$$

Abbreviations/Units: eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2); S_{Cr} = standardized serum creatinine (mg/dL); $K = 0.7$ (females); $\alpha = -0.329$ (females); min = indicates the minimum of S_{Cr}/K or 1; max = indicates the maximum of S_{Cr}/K or 1; age (years)

Coagulation Tests

- Prothrombin time (PT)/International normalized ratio (INR)
- Activated partial thromboplastin time (aPTT)
- Fibrinogen
- D-dimer
- Factor VII

Serum Inflammation Marker

- C-reactive protein

Urinalysis (microscopic)

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

Serum or Urine Pregnancy Test (ß-hCG): women of child-bearing potential

Serology Tests

- Hepatitis A (hepatitis a virus immunoglobulin M positive)
- Hepatitis B (hepatitis B virus [HBV] surface antigen positive)
- Hepatitis C (hepatitis C virus [HCV] antibody positive, confirmed by HCV RNA).
  - Subjects with HCV with undetectable virus after treatment are eligible. Subjects with a prior history of HBV are eligible if quantitative PCR for HBV DNA is negative.
- HIV

Plasma Samples for PK

- Area under the plasma concentration-time curve (AUC_{0-24}, $AUC_{0-\infty}$)
- Maximum observed concentration (C_{max})
- Time to maximum observed concentration (T_{max})
- Terminal elimination half-life ($T_{1/2}$)

Blood Response Biomarkers

- Genetic analyses (sequencing) of tumor tissues for mutations relevant to bromodomain inhibition
- Histochemical and/or protein analysis of tumor, plasma tissue, peripheral blood cells for changes relevant to bromodomain inhibition
- Genomic analysis and expression arrays may also be performed for exploratory purposes
- RNA sequencing
- Serum protein and cytokine analysis

Paired Biopsy Tissue Response Biomarkers

- c-Myc
- DNA or RNA sequencing
- Gene expression
- Other response or resistance biomarkers as appropriate

Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, the definitive list of analyses remains to be determined, and may include additional markers of macrophage activity, in addition to antitumor biomarkers that may be related to PLX2853 treatment.

APPENDIX 2: EXAMPLES OF STRONG CYP3A4 AND/OR 2C8 INHIBITORS AND INDUCERS

- Apalutamide
- Avanafil
- Boceprevir
- Carbamazepine
- Clarithromycin
- Clopidogrel
- Cobicistat
- Conivaptan
- Danoprevir and ritonavir
- Ebastine
- Elvitegravir and ritonavir
- Enzalutamide
- Gemfibrozil
- Grapefruit juice
- Ibrutinib
- Idelalisib
- Indinavir
- Itraconazole
- Ketoconazole
- Lomitapide
- Lopinavir and ritonavir
- Mitotane
- Naloxegol
- Nefazodone
- Nelfinavir
- Paritaprevir and ritonavir and ombitasvira and/or dasabuvir
- Phenytoin
- Posaconazole
- Repaglinide
- Rifampin
- Ritonavir
- Saquinavir
- St. John's wort
- Tacrolimus
- Telaprevir
- Telithromycin
- Troleandomycin
- Voriconazole

This list is not comprehensive and subject to change and all medications should be reviewed prior to administering. Please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers for further information.

APPENDIX 3: 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 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

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

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

Non-measurable tumor lesions

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

Special considerations regarding lesion measurability

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

Bone lesions:

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

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, 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 enrollment it is known that a subject 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 subjects 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 subject should be considered not evaluable from that point forward.**

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

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following 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 subject 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 CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

Tumor Response Evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least 1 measurable lesion (as detailed above in this Appendix 3). 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 subjects having non-measurable disease only are also eligible.

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

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 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 subjects have only 1 or 2 organ sites involved a maximum of 2 (1 site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image

is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

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

Response criteria

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

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if 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 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

Special notes on assessment of progression of non-target disease

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

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

When the subject 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 subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have

objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be **substantial**.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show 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 subject who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

(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 subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either 1 the 'best overall response'. This is described further below.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 10 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, Table 11 is to be used.

Missing assessments and not-evaluable designation

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

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

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

Best overall response: all time points

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

Table 10: Time Point Response: Subjects 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; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease

Table 11: Time Point Response: Subjects with Non-target Disease Only

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

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

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

Table 12: 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; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease

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

Special notes on response assessment

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Table 10, Table 11, and Table 12.

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.

APPENDIX 4: DRUGS CLEARLY ASSOCIATED WITH THE RISK OF TORSADES DE POINTES (TDP) AND QT PROLONGATION

Anti-arrhythmics
- Amiodarone
- Disopyramide
- Dofetilide
- Dronedarone
- Flecainide
- Ibutilide
- Procainamide (Oral off US Market)
- Quinidine
- Sotalol
- Ritonavir
- Indinavir
- Nelfinavir

Antimicrobials
- Azithromycin
- Ciprofloxacin
- Clarithromycin
- Erythromycin
- Grepafloxacin (Off Market worldwide)
- Levofloxacin
- Moxifloxacin
- Sparfloxacin (Removed from US Market)
- Pentamidine
- Fluconazole

Anti-psychotics
- Haloperidol
- Mesoridazine (Removed from US Market)
- Pimozide
- Thioridazine
- Chlorpromazine
- Droperidol
- Sulpiride (On non US Market)

Anti-cancers
- Arsenic trioxide
- Vandetanib

Anti-depressants, SSRIs
- Citalopram
- Escitalopram

Antihistamines
- Astemizole (Removed from US Market)
- Terfenadine (Removed from US Market)

Anti-malarials
- Chloroquine
- Halofantrine

Antilipemic
- Probucol (Removed from US Market)
- Ondansetron

Opiates
- Levomethadyl acetate (Removed from US Market)
- Methadone

Anesthetics, general
- Propofol
- Sevoflurane

Others
- Cisapride (Removed from US Market)
- Cocaine
- Anagrelide
- Bepridil (Removed from US Market)
- Domperidone (On non US Market)

This list is not comprehensive and all medications should be reviewed prior to administering. CredibleMeds® OncoSupport™ can be used as a reference for additional information of drugs with known TdP risk.

APPENDIX 5: ECOG PERFORMANCE STATUS

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

ECOG PERFORMANCE STATUS*

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

* As published in Oken 1982.

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

Revised: July 27, 2006

APPENDIX 6: EVALUATION OF PROGRESSION ACCORDING TO CA-125

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria and Table 13:

A. Subjects with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 ≥2 × the upper limit of the reference range on 2 occasions at least 1 week apart

   OR

B. Subjects with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 ≥2 × the nadir value on 2 occasions at least 1 week apart

   OR

C. Subjects with CA-125 in the reference range before treatment must show evidence of CA-125 ≥2 × the upper limit of the reference range on 2 occasions at least 1 week apart.

CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted. Subjects are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura (e.g., paracentesis) during the previous 28 days.

A subject may be declared to have progressive disease on the basis of either the objective RECIST 1.1 criteria or the CA-125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

Table 13: Definition of Progression After First-Line Therapy in Ovarian Cancer as Proposed by the GCIG

GCIG Subcategorized Group	RECIST Measurable/Nonmeasurable Disease		CA-125[a]
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of diameters (RECIST 1.1 definition) or Any new lesions (measurable or nonmeasurable) or Unequivocal increase in nontarget disease Date of PD: date of documentation of increase or new lesions	AND/OR	CA-125 ≥2 × ULRR on 2 occasions[b] Date of PD: first date of the CA-125 elevation to ≥2 × ULRR
B	As for A		CA-125 ≥2 × nadir value on 2 occasions[b] Date of PD: first date of the CA-125 elevation to ≥2 × nadir value
C	As for A		As for A

Source: Rustin 2011

CA-125 = cancer antigen 125; GCIG = Gynecological Cancer Intergroup; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; ULRR = upper limit of response range

Note: GCIG Groups A, B, and C defined above.

[a] CA-125 levels sampled after subjects received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days should not be taken into account.

[b] Repeat CA-125 any time but normally not less than 1 week after the first elevated CA-125 level.