CLINICAL STUDY PROTOCOL

Protocol Number:	PLX124-04
Title:	A Multicenter, Open-Label, Parallel, Phase 1b/2a Study of PLX2853 in Combination with Abiraterone Acetate and Prednisone and Phase 1b/2a Study of PLX2853 in Combination with Olaparib in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Indication:	mCRPC with progression currently receiving initial treatment with abiraterone acetate and prednisone; deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC with progression after treatment with abiraterone acetate/prednisone or with enzalutamide
Phase:	1b/2a
Sponsor:	Plexxikon Inc. 329 Oyster Point Blvd. South San Francisco, CA 94080, USA Telephone: (510) 647-4000
IND Number:	151,392
EudraCT Number:	2020-002021-28
Therapeutic Area:	Oncology
Medical Monitor:	

Protocol History

Date/Version:	26 Jun 2020/Original 07 Aug 2020/Amendment 1 17 Aug 2020/Amendment 1.1 (UK only) 25 Aug 2020/Amendment 2 29 Oct 2021/Amendment 3

SPONSOR SIGNATURE

Protocol PLX124-04:	A Multicenter, Open-Label, Parallel, Phase 1b/2a Study of PLX2853 in Combination with Abiraterone Acetate and Prednisone and Phase 1b/2a Study of PLX2853 in Combination with Olaparib in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Sponsor:	Plexxikon Inc. 329 Oyster Point Blvd. South San Francisco, CA 94080, USA Telephone: (510) 647-4000

I have read and approved this protocol.

11/3/2021
Date

INVESTIGATOR AGREEMENT AND SIGNATURE

Protocol PLX124-04:	A Multicenter, Open-Label, Parallel, Phase 1b/2a Study of PLX2853 in Combination with Abiraterone Acetate and Prednisone and Phase 1b/2a Study of PLX2853 in Combination with Olaparib in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Sponsor:	Plexxikon Inc. 329 Oyster Point Blvd. 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 Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

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

Principal Investigator Signature	Date

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

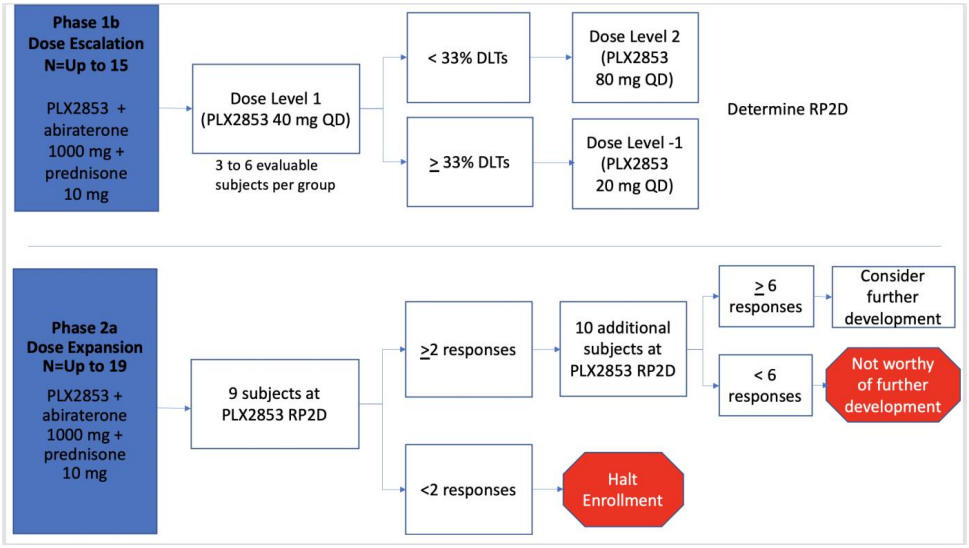
Abbreviation or Term	Definition/Explanation
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	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 measurable concentration postdose
BCRP	breast cancer resistance protein
BET	bromodomain and extra terminal domain
BRD	bromodomain-containing protein
CFR	Code of Federal Regulations
CI	confidence interval
CI_{90}	90% confidence interval
CI_{95}	95% confidence interval
CL	clearance
C_{max}	maximum observed concentration
CLIA	Clinical Laboratory Improvement Amendments
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	c-reactive protein
CT	computed tomography
CTC	circulating tumor cell
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
FDG PET	(18)F-fluorodeoxyglucose positron-emission tomography

Abbreviation or Term	Definition/Explanation
FU	follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HNSTD	highest non-severely toxic dose
HPLC	high performance liquid chromatography
IBW	ideal body weight
IC	inhibitory concentration
ICH	International Council for Harmonisation
IND	Investigational New Drug
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous, intravenously
K_d	dissociation constant
LC/MS/MS	liquid chromatography tandem mass spectrometry
mCRPC	metastatic castration-resistant prostate cancer
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NOAEL	no-observed-adverse-effect level
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
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease or pharmacodynamic
PFS	progression-free survival
PG	pharmacogenomics
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
QD	once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula

Abbreviation or Term	Definition/Explanation
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SSRE	Symptomatic Skeletal-Related Events
$T_{1/2}$	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
UV	ultraviolet

PROTOCOL SYNOPSIS

Title:	A Multicenter, Open-Label, Parallel, Phase 1b/2a Study of PLX2853 in Combination with Abiraterone Acetate and Prednisone and Phase 1b/2a Study of PLX2853 in Combination with Olaparib in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Sponsor:	Plexxikon Inc.
Clinical Phase:	Phase 1b/2a
Indication:	For PLX2853, abiraterone acetate, and prednisone combination: mCRPC with progression while currently receiving initial treatment with abiraterone acetate and prednisone For PLX2853 and olaparib combination: deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC with progression after treatment with abiraterone acetate/prednisone or with enzalutamide
Objectives:	**PLX2853 + Abiraterone Acetate + Prednisone Combination** **Phase 1b:** Primary Objectives • To evaluate the safety and tolerability of PLX2853 + abiraterone acetate + prednisone including dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone Secondary Objectives • To characterize the PK of PLX2853 and abiraterone and efficacy of PLX2853 combined with abiraterone acetate + prednisone in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone **Phase 2a:** Primary Objectives • To evaluate the efficacy of PLX2853 + abiraterone acetate + prednisone at the RP2D in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone Secondary Objectives • To further characterize the safety and PK of PLX2853 and abiraterone when PLX2853 is combined with abiraterone acetate + prednisone in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone **PLX2853 + Olaparib Combination** **Phase 1b:** Primary Objectives • To evaluate the safety and tolerability of PLX2853 + olaparib including dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide Secondary Objectives • To characterize the PK of PLX2853 and olaparib and efficacy of PLX2853 combined with olaparib in subjects with deleterious or suspected deleterious germline or

	somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide **Phase 2a:** Primary Objective • To evaluate the efficacy of PLX2853 + olaparib at the RP2D in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide Secondary Objectives • To further characterize the safety and PK of PLX2853 and olaparib when PLX2853 is combined with olaparib in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide **Exploratory Objectives – Both Phases, Both Combinations** • To assess biomarkers in peripheral blood cells, tumor cells, and tissue biopsies • To further evaluate the pharmacodynamics (PD) of PLX2853
Study Design:	**PLX2853 + Abiraterone Acetate + Prednisone Combination – Ph1b/2a Study Design** This multicenter, open-label, 2-part study will evaluate the safety, PK, PD, and efficacy of PLX2853 + abiraterone acetate + prednisone combination therapy in subjects with mCRPC who develop disease progression, while currently receiving initial abiraterone acetate and prednisone therapy, as documented by radiographic imaging, prostate-specific antigen (PSA), or clinical assessment. The study schema is presented below.  **Phase 1b: Dose Escalation** In Phase 1b (dose escalation), the safety profile, RP2D/MTD, PK, and PD of PLX2853 (administered orally once daily) in combination with abiraterone acetate (administered orally once daily) and prednisone (administered orally twice daily) in 21-day treatment cycles will be evaluated. Each cohort will be enrolled and assessed using a standard "3+3" design. The rules for determining DLT and dose escalation are defined further below.

The provisional dose escalation plan is detailed as follows:

Provisional PLX2853 Dose Escalation Plan			
Dose Level	**PLX2853 Dose (mg/day)[a]**	**Abiraterone Acetate Dose (mg/day)[a]**	**Prednisone Dose (total mg/day)[b]**
-1	20	1000	10
1	40	1000	10
2	80	1000	10

[a] Once daily (QD) dosing schedule unless otherwise specified. Initial cohort will assess QD dosing. Subsequent cohorts may evaluate alternative dosing regimens as agreed to by the Study Committee.

[b] 5 mg twice daily (BID) dosing schedule.

DLTs will be assessed in the first 21-day treatment cycle. In the absence of a DLT and in conjunction with review of the safety, PK, and available PD data from each dose cohort by the Study Committee, dose escalations are planned to occur in the following manner:

- A minimum of 3 to 4 subjects will be initially enrolled in Dose Level 1 (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 subjects (or ≥33% of the cohort) at a dose level, the dose at which this occurs will be considered intolerable and the MTD to have been exceeded. The highest dose level at which 0 or 1 of 6 subjects experience a DLT will be declared the RP2D.
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be studied. If that dose level is intolerable, the study will be halted.
- At least 6 subjects must be evaluable at a given dose level in order to be considered an RP2D.
- An RP2D may be declared at a dose level without reaching an MTD if further dose escalation is deemed unwarranted.
- Any subject who misses more than 25% of doses in Cycle 1 (e.g., ≥6 doses of PLX2853 in 21 days) for reasons other than a treatment-related adverse event (AE), or is withdrawn from the study prior to completing Cycle 1 for reasons other than a DLT, will not be DLT evaluable and additional subject(s) may be enrolled to provide adequate data for dose escalation decision making.

After dosing has been completed in each cohort, safety, PK data, and PD 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 PD (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 21 days. Once all ongoing subjects in a dose cohort have been treated for at least two 21-day 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 a Grade 3 or higher treatment-related toxicity and have completed 2 cycles of PLX2853. Any intra-subject dose escalation requires a discussion and agreement with the Medical Monitor.

Phase 2a: Dose Expansion

In Phase 2a, efficacy as well as additional safety, PK, and PD information of PLX2853 in combination with abiraterone acetate and prednisone at the RP2D dose established in Phase 1b by the Study Committee will be obtained using a Simon's 2-stage design.

Initially, 9 subjects will be enrolled to assess for efficacy in Phase 2a. If 2 or more responses are observed in the first 9 evaluable subjects, an additional 10 evaluable subjects will be enrolled. Subjects in Phase 2a who do not complete their 12-week disease response assessment for reasons other than toxicity or disease progression may be replaced.

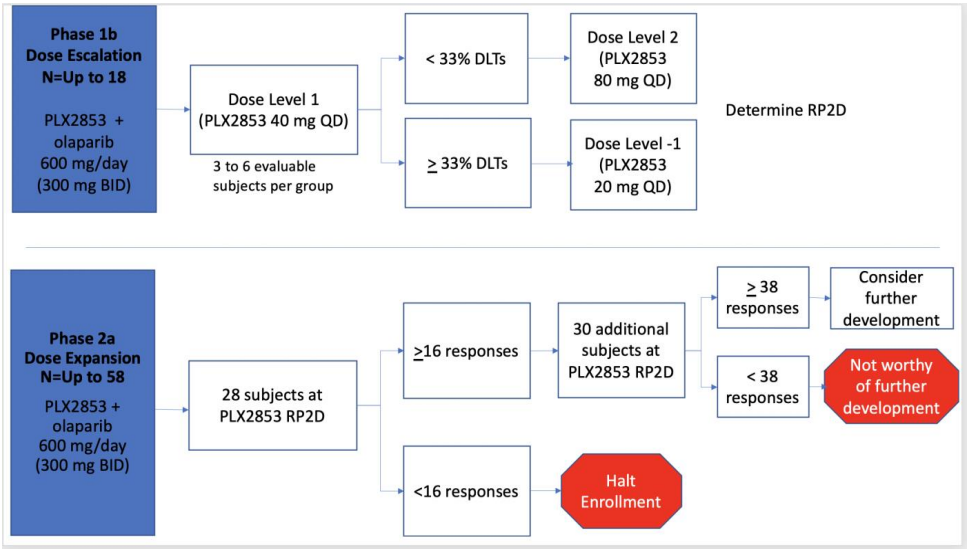
Pharmacokinetics of PLX2853 and Abiraterone

PLX2853 and abiraterone PK data will be analyzed in each dosing cohort for maximum observed concentration (C_{max}), AUC, and accumulation 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 of PLX2853 may be studied, such as alternate day dosing (e.g., every other day) depending on emerging safety and PK data.

PLX2853 + Olaparib Combination – Ph1b/2a Study Design

This multicenter, open label 2-part study will evaluate the safety, PK, PD, and efficacy of PLX2853 + olaparib combination therapy in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed, as documented by radiographic imaging, prostate-specific antigen (PSA), or clinical assessment, following prior treatment with abiraterone acetate and prednisone or with enzalutamide. This combination will only be investigated in regions where olaparib is approved.

The study schema is presented below.



Phase 1b: Dose Escalation

In Phase 1b, the safety profile, RP2D/MTD, PK, and PD of PLX2853 (administered orally once daily) in combination with olaparib (administered orally twice daily) in 21-day treatment cycles will be evaluated. Each cohort will be enrolled and assessed using a standard "3+3" design. The rules for determining DLT and dose escalation are defined further below.

The provisional dose escalation plan is detailed as follows:

Provisional PLX2853 Dose Escalation Plan		
Dose Level	**PLX2853 Dose (mg/day)[a]**	**Olaparib (total mg/day)[b]**
-1	20	600
1	40	600
2	80	600

[a] Once daily (QD) dosing schedule unless otherwise specified. Initial cohort will assess QD dosing. Subsequent cohorts may evaluate alternative dosing regimens as agreed to by the Study Committee.

[b] 300 mg twice daily (BID) dosing schedule.

DLTs will be assessed in the first 21-day treatment cycle. In the absence of a DLT and in conjunction with review of the safety, PK, and available PD data from each cohort by the Study Committee, dose escalation is planned to occur in the following manner:

- A minimum of 3 to 4 subjects will be initially enrolled in Dose Level 1 (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 subjects (or ≥33% of the cohort) at a dose level, the dose at which this occurs will be considered intolerable and the MTD to have been exceeded. The highest dose level at which 0 or 1 of 6 subjects experience a DLT will be declared the RP2D.
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be studied. If that dose level is intolerable, the study will be halted.
- At least 6 subjects must be evaluable at a given dose level in order to be considered an RP2D.
- An RP2D may be declared at a dose level without reaching an MTD if further dose escalation is deemed unwarranted.
- Any subject who misses more than 25% of doses in Cycle 1 (e.g., ≥6 doses of PLX2853 in 21 days) for reasons other than a treatment-related AE, or is withdrawn from the study prior to completing Cycle 1 for reasons other than a DLT, will not be DLT evaluable and additional subject(s) may be enrolled to provide adequate data for dose escalation decision making.

After dosing has been completed in each cohort, safety, PK data, and PD 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 PD (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 21 days. Once all ongoing subjects in a dose cohort have been treated for at least two 21-day 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 a Grade 3 or higher treatment-related toxicity and have completed 2 cycles of PLX2853. Any intra-subject dose escalation requires a discussion and agreement with the Medical Monitor.

Phase 2a: Dose Expansion

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

	Initially, 28 subjects will be enrolled to assess for efficacy in Phase 2a. If 16 or more responses are observed in the first 28 evaluable subjects, an additional 30 evaluable subjects will be enrolled. Subjects in Phase 2a who do not complete their 12-week disease response assessment for reasons other than toxicity or disease progression may be replaced. **Pharmacokinetics of PLX2853 and Olaparib** PLX2853 and olaparib PK data will be analyzed in each dosing cohort for maximum observed concentration (C_{max}), AUC, and accumulation 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 of PLX2853 may be studied, such as alternate day dosing (e.g., every other day) depending on emerging safety and PK data.
Number of Subjects:	Up to 110 evaluable subjects will be enrolled in the study, as follows. **PLX2853 + Abiraterone Acetate + Prednisone Combination** • **Phase 1b: Up to 15 evaluable subjects** Approximately 9 to 15 evaluable subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone • **Phase 2a: Up to 19 evaluable subjects** There will be a single Simon's 2-stage design cohort of between 9 to 19 evaluable subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone **PLX2853 + Olaparib Combination** • **Phase 1b: Up to 18 evaluable subjects** Approximately 9 to 18 evaluable subjects, with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate or enzalutamide. • **Phase 2a: Up to 58 evaluable subjects** There will be a single Simon's 2-stage design cohort of between 28 to 58 evaluable subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate or enzalutamide
Inclusion Criteria:	**Inclusion Criteria Applicable to Both Combinations:** 1. Age ≥18 years at the time of signing informed consent. 2. Histologically confirmed adenocarcinoma of the prostate with tumor tissue available for molecular analyses. 3. Serum testosterone level of <50 ng/dL (<2.0 nM) assessed within 28 days of C1D1 and surgically or medically castrated and/or receiving treatment with an LHRH/GnRH analogue (agonist/antagonist). 4. Subjects must continue primary androgen deprivation with an LHRH/GnRH analogue (agonist/antagonist) or have received an orchiectomy. If receiving primary androgen deprivation therapy, this therapy must have been initiated at least 28 days prior to start of study dosing and must be continued throughout the study. 5. Eastern Cooperative Oncology Group Performance Status 0 to 1.

6. Adequate organ function as demonstrated by the following laboratory values. All Screening laboratory tests should be performed within 10 days prior to the first PLX2853 dose.
   - Hematological:
     - Neutrophils ≥1500/µL.
     - Platelets ≥100,000/µL (transfusion not permitted within 28 days prior to screening blood draw for olaparib, 14 days for abiraterone).
     - Hemoglobin ≥9 g/dL (transfusion and erythropoietin not permitted within 28 days prior to screening blood draw for olaparib, 14 days for abiraterone).
   - Renal:
     - Measured (by 24-hour urine collection) or calculated Creatinine Clearance (CrCL) >50 mL/min. The Cockcroft-Gault formula should be used for calculation (Appendix 1).
   - Hepatic:
     - Serum total bilirubin ≤1.5 × upper limit of normal (ULN).

       Exception for elevated bilirubin secondary to Gilbert's disease. 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 × ULN.

       For subjects with metastatic liver metastases ≤2.5 × ULN.
   - Coagulation:
     - International normalized ratio (INR) ≤1.5 × ULN.
     - Activated partial thromboplastin time (aPTT) ≤1.5 × ULN.
   - Chemistry:
     - Albumin ≥3.0 g/dL.
7. Fertile male subjects with female sexual partners must agree to use a highly effective method of birth control (defined in Section 4.2.1) during the study and for 90 days after the last dose of study drug.
8. Except as specified above for organ function, all drug-related toxicity from previous cancer therapy (including ongoing abiraterone acetate + prednisone therapy if applicable) must be resolved (to Grade ≤1 or baseline per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) prior to study treatment administration (Grade 2: alopecia, hot flashes, decreased libido, or neuropathy is allowed).
9. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

Inclusion Criteria Applicable to PLX2853 + Abiraterone Acetate + Prednisone Combination:

10. Currently receiving initial abiraterone acetate 1000 mg QD and prednisone per abiraterone acetate label as most recent systemic therapy for mCRPC and showing evidence of progression as assessed by the investigator with one or more of the following (Subjects who begin treatment in the hormone sensitive setting and progress to mCRPC and have not discontinued their initial abiraterone acetate treatment are not excluded). Subjects must be on a stable dose of prednisone for at least 14 days prior to C1D1:

	a. PSA progression defined, per PCWG3 criteria (Scher 2016; Appendix 6) at trial entry, as ≥2 occurrences of rising PSA levels with a minimum interval of 1 week and a PSA concentration of ≥1 ng/mL if confirmed PSA rise is the only measure of progression. b. Worsening measurable disease on CT/MRI per RECIST v1.1 criteria or at least one new documented bone lesion on a bone scan. 11. Potassium within normal limits. **Inclusion Criteria Applicable to PLX2853 + Olaparib Combination:** 12. Prior genetic testing completed with known deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutation per FDA label for mCRPC as defined by an FDA-approved companion diagnostic (HRR mutation must be known prior to consent). 13. Prior treatment with abiraterone acetate and/or enzalutamide for metastatic prostate cancer and/or CRPC. 14. Evidence of radiographic progression of metastatic disease at study entry as assessed by the investigator defined as measurable disease on CT/MRI per RECIST v1.1 criteria or at least one documented bone lesion on a bone scan. Subjects whose disease spread is limited to regional pelvic lymph nodes or local recurrence (e.g., bladder, rectum) are not eligible.
Exclusion Criteria:	**Exclusion Criteria Applicable to Both Combinations:** 1. Prior exposure to a bromodomain inhibitor. 2. Ongoing systemic infection requiring antibiotic, antiviral, or antifungal treatment. 3. History of 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. Symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable and asymptomatic. 6. Known or suspected allergy to the investigational agent or any agent given in association with this study. 7. 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 TdP can be found in Appendix 4. • QTcF ≥450 msec at Screening (based on average of triplicate ECGs at baseline). o 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 or left ventricular ejection fraction measurement of <50% at baseline. Subjects must not have unstable angina

	(anginal symptoms at rest) or new-onset angina within the last 3 months or have had a coronary artery bypass, angioplasty, vascular stent, or myocardial infarction within the past 6 months. • Uncontrolled hypertension, defined as systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg which 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). 8. 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. 9. Non-healing wound or ulcer. 10. 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. 11. 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. These subjects must be willing to undergo additional testing per local standard of care. 12. Baseline moderate or severe hepatic impairment (Child-Pugh Class B and C). 13. Active known second malignancy with the exception of any of the following: • Adequately treated basal cell carcinoma or squamous cell carcinoma of the skin. • 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. 14. Major surgery or significant traumatic injury within 28 days of Cycle 1 Day 1. 15. Currently receiving medications known to be strong or moderate inducers or inhibitors of CYP3A4 and substrates of CYP2D6 with a narrow therapeutic window (Appendix 2). These strong and moderate inducers, inhibitors and substrates must be discontinued at least 7 days prior to the first administration of study drug). 16. 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. 17. Any chronic medical condition requiring a dose of corticosteroids greater than 10 mg prednisone/prednisolone daily. 18. 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. 19. Subjects with a history of adrenal insufficiency, hyperaldosteronism, or pituitary dysfunction.

20. Poorly controlled known type 2 diabetes with HbA1C >7.5% (must be assessed within 28 days of C1D1 for all subjects with known type 2 diabetes).
21. Live vaccine within 4 weeks of starting treatment.
22. Treatment with warfarin within 7 days of C1D1.
23. Subject is participating in any other therapeutic clinical study (observational or registry studies are allowed).
24. 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 in the study in the judgment of the Investigator.

Exclusion Criteria Applicable to PLX2853 + Abiraterone Acetate + Prednisone Combination:

25. Receipt of any anti-cancer therapy prior to Cycle 1 Day 1 with the exception of abiraterone acetate and GnRH therapy:
    - Prior systemic chemotherapy in the setting of mCRPC is not permitted (prior chemotherapy in the hormone-sensitive setting is allowed provided last dose was at least 6 months prior to Cycle 1 Day 1). Prior chemotherapy for any other disease within 2 years is prohibited.
    - Radiation therapy within 14 days prior to Cycle 1 Day 1.
    - Small molecule anti-cancer therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.
    - Immunotherapy 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) prior to Cycle 1 Day 1.
    - 5-α reductase inhibitors (e.g., finasteride, dutasteride), estrogen compounds (including estramustine) and megesterol are considered to be anti-cancer agents and prohibited within 21 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.

    Note: Subjects can receive a stable dose of bisphosphonates or denosumab for bone metastases before and during the study, as long as these were started at least 4 weeks prior to treatment with study drug.

Exclusion Criteria Applicable to PLX2853 + Olaparib Combination:

26. A medical history that includes any of myelodysplastic syndrome, monoclonal gammopathy of undetermined significance or acute myeloid leukemia.
27. Receipt of any anti-cancer therapy prior to Cycle 1 Day 1 with the exception of GnRH therapy:
    - Radiation therapy within 14 days prior to Cycle 1 Day 1.
    - Small molecule anti-cancer therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.
    - Immunotherapy 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) prior to Cycle 1 Day 1.
    - 5-α reductase inhibitors (e.g., finasteride, dutasteride), estrogen compounds (including estramustine) and megesterol are considered to be anti-cancer agents and prohibited within 21 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.

	• Prior treatment with DNA-damaging cytotoxic chemotherapy (including platinum-based agents, cyclophosphamide, and mitoxantrone) is excluded with the exception of estramustine. Non-DNA-damaging chemotherapy (docetaxel, cabazetaxel, etc.) within 14 days or 5 half-lives (whichever is shorter) is excluded. Any chemotherapy not listed requires Medical Monitor review and approval to confirm eligibility. Note: Subjects can receive a stable dose of bisphosphonates or denosumab for bone metastases before and during the study as long as these were started at least 4 weeks prior to treatment with study drug. 28. Prior exposure to a PARP inhibitor.
Duration of Study:	**Screening:** • Up to 28 days prior to the first dose of study drug **Treatment Period:** • Daily in 21-day treatment cycles until subject discontinuation or withdrawal or study termination **30-Day Follow-Up 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 Visits:** • Subjects will be followed until death, withdrawal of consent, or loss to follow-up according to the following schedule: ▪ First two 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. Response assessment during follow-up will include at minimum the modality used to determine response (radiographic imaging, PSA, and/or CTC assessment).
Test Products, Doses, and Mode of Administration:	**PLX2853** PLX2853 is formulated as 20-mg strength tablets for oral use. Subjects should fast for 2 hours before and 1 hour after taking PLX2853. Doses will be taken orally with water. PLX2853 should be taken at approximately the same time each day. PLX2853 tablets 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. **Abiraterone Acetate** Abiraterone acetate 1000 mg is administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone acetate (ZYTIGA® or generic equivalent) is available as either 500 mg film-coated tablets or 250 mg uncoated tablets. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. The tablets should be swallowed whole with water and not be crushed or chewed. Please refer to the ZYTIGA® FDA label or SmPC for additional information. PLX2853 and abiraterone acetate should be taken at the same time.

	Prednisone Prednisone 5 mg tablets are administered per the label for abiraterone acetate. Prednisone is recommended to be taken with food or milk at least 2 hours before PLX2853 and abiraterone acetate or 1 hour after taking PLX2853 and abiraterone acetate, except for PK collection days when subjects should take prednisone with food or milk at least 1 hour after taking PLX2853 and abiraterone acetate. An equivalent approved steroid may be used where applicable (prednisolone is acceptable; other equivalent agents must be approved by the Plexxikon Medical Monitor). **Olaparib** Olaparib 300 mg is administered orally twice daily. The morning dose of olaparib should be taken at the same time as PLX2853 and subjects should fast for at least 2 hours before and 1 hour after taking PLX2853 and olaparib. The evening olaparib dose may be taken with or without food. The tablets should be swallowed whole with water and not be chewed, crushed, dissolved, or divided. Olaparib tablets are available in 2 strengths, 100 mg and 150 mg. Please refer to the LYNPARZA® FDA label for additional information. PLX2853 and olaparib (morning dose) should be taken at the same time.
Definition of Dose-limiting Toxicity (DLT) (Phase 1b PLX2853, abiraterone acetate, and/or prednisone, and Phase 1b PLX2853 and/or olaparib)	DLTs are defined as clinically significant AEs or laboratory abnormalities occurring during the first cycle (21 days) of study drug administration that are *at least possibly related* to any study drug (PLX2853, abiraterone acetate, olaparib, or prednisone), and that meet one of the following CTCAE v5.0 criteria below. DLTs will be evaluated for each cohort. DLTs will be assessed during a DLT assessment window of 21 days in Cycle 1. Toxicities occurring in treatment Cycle 2 or later will be reviewed and their impact on dose escalation and dosing frequency assessed. If during the DLT window a subject requires treatment with a concomitant medication that results in a dose reduction of abiraterone acetate or olaparib (per their label), the patient will be considered inevaluable, unless the AE requiring treatment meets the definition of a DLT. In Phase 1, a subject who misses greater than 25% of their expected doses in Cycle 1, or does not complete Cycle 1, for reasons other than a related toxicity will be considered inevaluable and may be replaced. DLTs will be determined based on the following criteria: **Hematologic Toxicities** • Grade 4 neutropenia lasting >5 days • Febrile neutropenia • Grade 4 thrombocytopenia of any duration • Grade ≥3 thrombocytopenia associated with clinically significant hemorrhage for any duration • Grade 4 anemia **Non-Hematologic Toxicities** • A dose reduction required during Cycle 1 due to an AE (except as specified above) • AE related treatment delays causing a subject to miss at least 25% of their total expected doses of any drug in the combination during Cycle 1 • Any Grade ≥3 non-hematologic toxicity of any duration, except: ▪ Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours ▪ Grade 3 fatigue lasting <5 days ▪ Grade 3 hypertension that can be controlled with medical therapy ▪ An increase of indirect (unconjugated) bilirubin indicative of M. Meulengracht/Gilbert's syndrome

	▪ Serum lipase and/or serum amylase Grade 3 ≤7 consecutive days without clinical signs or symptoms of pancreatitis ▪ Grade 3 AST/ALT for <5 days ▪ Grade 3 neuropathy in subjects with pre-existing Grade 2 neuropathy • ALT/AST >3 x ULN with total bilirubin >2 x ULN without another explanation (e.g., cholestasis) • Any Grade 3 clinically significant electrolyte imbalance confirmed with repeat assessment within 24 hours. A subject who experiences a DLT may remain in the study and continue receiving PLX2853, abiraterone acetate, and prednisone or PLX2853 and olaparib 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 agreement by the Medical Monitor. If a subject is required to permanently discontinue at least one of the study medications for any reason they will be discontinued from all study treatment. For patients receiving abiraterone acetate, if PLX2853 and abiraterone acetate are withheld, then consideration should be given to tapering the dose of prednisone as clinically indicated. 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 (e.g., AEs meeting the criteria of a DLT occurring in Cycle 2 or later) are observed requiring dose reductions, 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 and abiraterone or olaparib will be assessed by measuring the AUC from time zero to time of last measurable concentration postdose ($AUC_{0\text{-last}}$), AUC from time zero to 24 hours postdose ($AUC_{0\text{-}24}$), 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, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate.
Biomarker and Pharmacodynamic (PD) Parameters:	Biomarker analyses for PD 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 CTC status and possibly other exploratory markers of response or resistance. Exploratory analysis of biomarker samples may also be performed to learn about the drug and disease properties.
Efficacy Parameters:	**Treatment response will be defined as:** • Objective response by RECIST v1.1 with a minimum interval for confirmation of CR and PR of 4 weeks and/or • PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later • Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline) **Treatment failure will be defined as:** • Progression by RECIST v1.1 and/or • Progression by bone scan with a confirmatory scan ≥6 weeks later and/or

	• PSA progression per PCWG3 (Scher 2016) (a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, occurring at least 12 weeks from start of treatment, and confirmed by a second consecutive value obtained at least three weeks later). PSA progression alone does not necessitate treatment discontinuation. The last value of PSA, CTC count, CT scan, and bone scan before the date of first study treatment (within 28 days for imaging; within 10 days for laboratory assessments) will be used as the baseline value for this assessment. In addition, the following parameters will be assessed: • Radiographic progression-free survival (rPFS) • Time to PSA progression • Duration of PSA response • Overall survival • PK parameters of PLX2853 and abiraterone and PLX2853 and olaparib following single and repeated dosing • Best Overall Response (BOR) per RECIST v1.1 • Duration of Response (DOR) • Time to first Symptomatic Skeletal-Related Event (SSRE)
Safety Parameters:	Safety variables to be assessed will include assessment of AEs, physical examinations, laboratory test results (hematology, clinical chemistry, coagulation, serum inflammation markers, and urinalysis), electrocardiogram, MUGA/ECHO, weight, and vital signs.
Endpoints:	**PLX2853 + Abiraterone Acetate + Prednisone Combination** **Phase 1b, Primary Endpoint:** • Incidence of DLTs, TEAEs, changes in safety parameters, and unacceptable toxicities **Phase 2a, Primary Endpoint:** • Response as defined by any of the outcomes listed below. If any of these occur, the subject will be considered to have responded. ▪ Objective response by per RECIST v1.1 with a minimum interval for confirmation of CR and PR of 4 weeks ▪ PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later ▪ Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline) **PLX2853 + Olaparib Combination** **Phase 1b, Primary Endpoint:** • Incidence of DLTs, TEAEs, changes in safety parameters, and unacceptable toxicities **Phase 2a, Primary Endpoint:** • Response as defined by any of the outcomes listed below. If any of these occur, the subject will be considered to have responded. ▪ Objective response by modified RECIST v1.1 with a minimum interval for confirmation of CR and PR of 4 weeks ▪ PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later

	▪ Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline) **Secondary Endpoints – Both Phases, Both Combinations** • Radiographic progression-free survival (rPFS) • Time to PSA progression • Duration of PSA response • Overall survival defined as the time from the first dose of study drug to the date of death due to any cause • Incidence of TEAEs, changes in safety parameters, and unacceptable toxicities • PK parameters of PLX2853 and abiraterone and PLX2853 and olaparib following single and repeated dosing • BOR per RECIST v1.1 • DOR (time from date of first documented, confirmed response using RECIST v1.1 and PCWG3 until date of documented progression or death from any cause). • Time to first SSRE defined as: ▪ Use of radiation therapy to prevent or relieve skeletal symptoms. ▪ Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation is required. ▪ Occurrence of spinal cord compression. Radiologic documentation required. ▪ Orthopedic surgical intervention for bone metastasis. **Exploratory Endpoints – Both Phases, Both Combinations** • Analysis of peripheral blood cells for dose- and exposure-dependent changes in the expression of BET target genes as measured by a 12-gene BET inhibitor responsive signature • Pharmacodynamic assessments for potential biomarkers
Statistical Considerations:	**Phase 1b (PLX2853 + Abiraterone Acetate + Prednisone Combination and PLX2853 + Olaparib Combination):** Both combinations will be evaluated in Phase 1b using a standard "3+3" design in order to determine the MTD/RP2D taking into consideration safety, PK, and PD 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. **Phase 2a (PLX2853 + Abiraterone Acetate + Prednisone Combination):** Efficacy of PLX2853 + abiraterone acetate + prednisone will be investigated in a cohort of subjects with mCRPC. Phase 2a will enroll up to 19 evaluable subjects using a Simon's 2-stage design in which initially 9 evaluable subjects are enrolled. If 2 or more responders are observed in 9 evaluable subjects, another 10 evaluable subjects will be enrolled for a total of 19 subjects. If 6 or more responders are observed, the study has 80% power with alpha of 0.05 to reject the RR of 15% in favor of the RR of 40%. Recruitment will stop if no more than 1 responder is observed after the initial 9 subjects have been accrued. ORR

	will be summarized along with a 95% confidence interval (CI). A 2-sided 95% CI will be calculated for the true response rate based on the Clopper-Pearson method. Response will be defined on the basis of the following outcomes, if any of these occur subjects will be considered to have responded: • Objective response by RECIST v1.1 with a minimum interval for confirmation of CR and PR of 4 weeks and/or • PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later • Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline) Safety, PK, and PD 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. **Phase 2a (PLX2853 + Olaparib):** Efficacy of PLX2853 + olaparib will be investigated in a cohort of subjects with mCRPC. Phase 2a will enroll up to 58 evaluable subjects using a Simon's 2-stage design in which initially 28 evaluable subjects are enrolled. If 16 or more responders are observed in 28 evaluable subjects, another 30 evaluable subjects will be enrolled for a total of 58 subjects. If 38 or more responders are observed, the study has 80% power with alpha of 0.05 to reject the RR of 54% in favor of the RR of 70%. Recruitment will stop if no more than 15 responders are observed after the initial 28 subjects have been accrued. ORR will be summarized along with a 95% confidence interval (CI). A 2-sided 95% CI will be calculated for the true response rate based on the Clopper-Pearson method. Response will be defined on the basis of the following outcomes, if any of these occur subjects will be considered to have responded: • Objective response by RECIST v1.1 and/or • PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later • Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline) Safety, PK, and PD 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.

SYNOPSIS TABLE 1: PHASE 1B PLX2853 + ABIRATERONE/PREDNISONE OR PLX2853 + OLAPARIB DOSE ESCALATION SCHEDULE OF EVENTS

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1				C2		C3	C4+[2]	30-day FU[3]	LTFU
	STUDY DAY►	-28 to -1	1	2	8	15	1	15	1	1		
	WINDOW (days)►				± 2	± 2	+ 3	± 3	± 5	± 5	± 7	± 14
Informed Consent		X										
History	Medical history	X										
	Demographics	X										
	Identification of HRR Defect (Olaparib only; historical testing)[4]	X										
Vital	Vital signs[5]	X	X	X	X	X	X	X	X	X	X	
	Height	X										
	Weight	X	X		X	X	X	X	X	X	X	
Safety	Physical exam[6]	X	X[7]		X	X	X	X	X	X	X	
	ECOG	X	X[7]		X	X	X	X	X	X	X	
	12-lead ECG[8,18]	X	X	X		X	X	X	X	X	X	
	ECHO or MUGA (abiraterone only)[9]	X										
Lab	PG sample	X										
	Hepatitis A, B and C, HIV[10]	X[1]										
	Hematology[11]	X[1]	X[7]		X	X	X	X	X	X	X	
	Chemistry[12]	X[1]	X[7]		X	X	X	X	X	X	X	
	Coagulation tests[13]	X[1]	X[7]		X	X	X	X	X	X	X	
	Hemoglobin A1c (Type 2 diabetics only)	X[30]										
	Testosterone	X[31]								X[31]		
	PSA	X[1]	X[7]				X		X	X	X	
	Circulating Tumor Cells[14]	X	X[7]							X[22]	X	X[27]
	Urinalysis[15]	X[1]	X[7]		X	X	X	X	X	X	X	
	Serum c-reactive protein	X[1]	X[7]		X	X	X		X	X	X	
	PK sample[16,17,18]		X	X		X	X	X	X	X	X	
	Biomarker (PD) blood sample[19]		X	X		X	X		X	X	X	

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1				C2		C3	C4+[2]	30-day FU[3]	LTFU
	STUDY DAY►	-28 to -1	1	2	8	15	1	15	1	1		
	WINDOW (days)►				± 2	± 2	+ 3	± 3	± 5	± 5	± 7	± 14
Medications, Non-drug Treatments, Radiotherapy	Prior treatment	X										
	Concomitant Medication Review	X										
AE	Adverse events[20]	X										
Treatment Response	Archival tissue sample	X										
	Paired biopsy for malignant lesion (optional)	X[28]					X					
	CT Scan[21]	X								X[22]		X[27]
	Bone Scan[21]	X								X[22]		X[27]
	SSRE evaluation	X										
Treatment	PLX2853 administration[16,23]		Daily administration for 21 days (full cycle)									
	Abiraterone acetate or olaparib administration[16,23]	X[29]	Abiraterone: QD administration for 21 days (full cycle) or Olaparib: BID administration for 21 days (full cycle)									
	Prednisone administration (abiraterone combo only)[16,24]	X[29]	BID administration for 21 days (full cycle)									
	Study drug compliance (diary review and accountability)[25]						X		X	X	X	
Survival	Survival follow-up[26]											X

30-day FU = 30-day follow-up visit; AE = adverse event; aPTT = activated partial thromboplastin time; AUC = area under the concentration-time curve; BID = twice daily; C = cycle; CTC = circulating tumor cells; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; LTFU = long-term follow-up visit; PD = pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetic; PSA = prostate-specific antigen; PT = prothrombin time; QD = once daily

1 Unless otherwise specified, all screening laboratory tests should be performed within 10 days of C1D1. 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 months may be given the option to only have study visits 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 Olaparib combination only: known HRR status assessed per standard of care testing (FoundationOne CDx or BRACAnalysis CDx are suggested). Results of test must be available prior to consent.

5 Vital signs must be obtained predose (PLX2853, abiraterone acetate, prednisone, and olaparib) on PK collection days.

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

7 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation, urinalysis, C-reactive protein, and PSA do not need to be repeated if these assessments from Screening occurred within 3 days of C1D1. CTC count does not need to be repeated if the assessment from Screening occurred within 10 days of C1D1 unless the screening sample was unable to be processed or 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.

8 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). Subjects must continue to meet eligibility criteria on C1D1 pre-dose assessment in order to proceed with dosing.

9 Abiraterone combination only: ECHO or MUGA will be performed in screening and as clinically indicated once on study.

10 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).

11 Hematology evaluation must include hemoglobin, hematocrit, and white blood cell count with differential and platelet count. A complete list of required tests is found in Appendix 1 to the protocol.

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

13 Coagulation evaluation must include PT/INR, aPTT, fibrinogen, d-dimer, and Factor VII. A complete list of required tests is found in Appendix 1 to the protocol.

14 Subjects with a positive CTC sample at baseline, as indicated by a value of at least 5 cells/7.5 mL blood, will continue to have CTC samples collected while on treatment at each radiographic assessment timepoint. If the baseline sample does not meet this criterion then no additional CTC samples will be collected after the subject has received their first dose of PLX2853.

15 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.

16 On PK days, subjects should be instructed not to take their study drug dose (PLX2853, abiraterone acetate, and prednisone or PLX2853 and olaparib) at home.

17 Additional samples for PK may be collected if a subject experiences a DLT, serious adverse event, AE of special interest, or at the Sponsor's request. Samples for PK should be collected for any dose modification at predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable) 2 weeks (± 1 week) after the modification or at the next scheduled clinic visit if occurs no less than 1 week after the modification. The time since the last dose of PLX2853 and abiraterone acetate or PLX2853 and olaparib should be noted.

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Assessment	**C1D1**	**C1D2**	**C1D15**	**C2+D1**	**C2D15**	**30-day FU**
ECG	Predose and at 0.5, 1, 2, 3, and 5 hours postdose	Predose	Predose and at 0.5, 1, 2, 3, and 5 hours postdose	Predose and 1 hour postdose at the start of each cycle	Predose and 1 hour postdose	Anytime
PK for PLX2853, abiraterone, and olaparib	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose	Predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable)	Predose, 1, and 3 hours postdose	Predose, 1, and 3 hours postdose	Anytime
PD	Predose, 3, and 5 hours postdose	Predose	Predose and 3 hours postdose	Predose	N/A	Anytime

Note: All PK and PD samples and ECGs 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 and PD samples should be collected after the corresponding ECGs have been obtained.

19 Multiple pharmacodynamics 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).

20 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.

21 CT (or MRI for subjects with a contraindication to contrast) should include at minimum chest, abdomen, and pelvis. Soft tissue progression is assessed per RECIST v1.1 and does not require a confirmatory scan. Progression per bone scan is assessed per PCWG3 and requires a confirmatory bone scan at least 6 weeks later.

22 Radiographic assessment of tumor burden will occur every 9 weeks (±7 days) for the first 24 weeks of treatment (pre-C4, pre-C7, pre-C10), or more frequently as clinically indicated. After C10, radiographic assessments will occur every 12 weeks (pre-C14, pre-C18, etc.), or more frequently as clinically indicated. CTCs will be assessed at every radiographic assessment as indicated in footnote 14.

23 PLX2853 and abiraterone acetate should be taken at the same time. PLX2853 and the morning dose of olaparib should be taken at the same time. Subjects should fast for 2 hours before and 1 hour after taking the PLX2853 and abiraterone acetate or olaparib, except for PK collection days as noted above. The evening dose of olaparib may be taken with or without food. The tablets should be swallowed whole with water and not be crushed or chewed.

24 Prednisone should be taken at least 2 hours before PLX2853 and abiraterone acetate or 1 hour after taking PLX2853 and abiraterone acetate, except for PK collection days when subjects should take prednisone 1 hour after taking PLX2853 and abiraterone acetate.

25 Collection of completed drug diary and distribution of new diary to occur at the beginning of each cycle.

26 Subjects will be followed until death, withdrawal of consent, or loss to follow-up – every 3 months for the first 2 years 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.

27 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. Response assessment in follow up will include at minimum the modality used to determine response (radiographic imaging, PSA, and/or CTC assessment).

28 If the subject agrees to participate in the optional paired biopsy collection and the archival tissue provided was collected within 2 months of Screening, a fresh sample does not need to be collected at Screening for the optional paired biopsy baseline sample. The paired biopsies should be from the same lesion if possible/feasible, and preferably from a non-target lesion.

29 Abiraterone/Prednisone Only: Subject must be receiving abiraterone acetate 1000 mg QD and prednisone 5–10 mg total daily dose at time of study entry.

30 Hemoglobin A1c evaluation is required within 28 days of C1D1 for all patients with confirmed or suspected Type 2 diabetes.

31 Serum testosterone evaluation is required within 28 days of C1D1 and all radiographic response timepoints while on study treatment (every 9 weeks for the first 24 weeks of treatment and then every 12 weeks).

SYNOPSIS TABLE 2: PHASE 2A PLX2853 + ABIRATERONE ACETATE/PREDNISONE OR PLX2853 + OLAPARIB DOSE EXPANSION SCHEDULE OF EVENTS

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1			C2		C3	C4+[2]	30-day FU[3]	LTFU
	STUDY DAY►	-28 to -1	1	8	15	1	15	1	1		
	WINDOW (days)►			± 2	± 2	± 3[3]	± 3	± 5	± 5	± 7	± 14
Informed Consent		X									
History	Medical history	X									
	Demographics	X									
	Identification of HRR Defect (Olaparib only)[4]	X									
Vital	Vital signs[5]	X	X	X	X	X	X	X	X	X	
	Height	X									
	Weight	X	X	X	X	X	X	X	X	X	
Safety	Physical exam[6]	X	X[7]	X	X	X	X	X	X	X	
	ECOG	X	X[7]	X	X	X	X	X	X	X	
	12-lead ECG[8]	X	X		X	X	X	X	X	X	
	ECHO or MUGA (abiraterone only)[9]	X									
Lab	PG sample	X									
	Hepatitis A, B and C, HIV[10]	X[1]									
	Hematology[11]	X[1]	X[7]	X	X	X	X	X	X	X	
	Chemistry[12]	X[1]	X[7]	X	X	X	X	X	X	X	
	Coagulation tests[13]	X[1]	X[7]	X	X	X	X	X	X	X	
	Hemoglobin A1c (Type 2 diabetics only)	X[30]									
	Testosterone	X[31]							X[31]		
	PSA	X[1]	X[7]			X		X	X	X	
	Circulating Tumor Cells[14]	X	X[7]						X[22]	X	X[27]
	Urinalysis[15]	X[1]	X[7]	X	X	X	X	X	X	X	
	Serum c-reactive protein	X[1]	X	X	X	X		X	X	X	
	PK sample[16,17,18]		X		X	X	X	X	X	X	
	Biomarker (PD) blood sample[19]		X		X	X		X	X	X	

ASSESSMENTS▼	PROCEDURE▼	SCR[1]	C1			C2		C3	C4+[2]	30-day FU[3]	LTFU
	STUDY DAY►	-28 to -1	1	8	15	1	15	1	1		
	WINDOW (days)►			± 2	± 2	± 3[3]	± 3	± 5	± 5	± 7	± 14
Medications, Non-drug Treatments, Radiotherapy	Prior treatment	X									
	Concomitant Medication Review	X									
AE	Adverse events[20]	X									
Treatment Response	Archival tissue sample	X									
	Paired biopsy for malignant lesion (optional)	X[28]				X					
	CT Scan[21]	X						X[22]			X[27]
	Bone Scan[21]	X						X[22]			X[27]
	SSRE evaluation	X									
Treatment	PLX2853 administration[16,23]		Daily administration for 21 days (full cycle)								
	Abiraterone acetate or olaparib administration[16,23]	X[29]	Abiraterone: QD administration for 21 days (full cycle) or Olaparib: BID administration for 21 days (full cycle)								
	Prednisone administration[16,24]	X[29]	BID administration for 21 days (full cycle)								
	Study drug compliance (diary review and accountability)[25]					X		X		X	
Survival	Survival follow-up[26]										X

30-day FU = 30-day follow-up visit; AE = adverse event; aPTT = activated partial thromboplastin time; AUC = area under the concentration-time curve; BID = twice daily; C = cycle; CTC = circulating tumor cell; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; LTFU = long-term follow-up visit; PD = pharmacodynamics; PG = pharmacogenomics; PK = pharmacokinetic; PSA = prostate-specific antigen; PT = prothrombin time; QD = once daily

1 Unless otherwise specified, all screening laboratory tests should be performed within 10 days of C1D1. 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 months may be given the option to only have study visits have study visits 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 Olaparib combination only: known HRR status assessed per standard of care testing (FoundationOne CDx or BRACAnalysis CDx are suggested). Results of test must be available prior to consent.

5 Vital signs must be obtained predose (PLX2853, abiraterone acetate, and prednisone) on PK collection days.

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

7 ECOG Performance Status, symptom-directed physical examination, hematology, chemistry, coagulation, urinalysis, C-reactive protein, and PSA do not need to be repeated if these assessments from Screening occurred within 3 days of C1D1. CTC count does not need to be repeated if the assessment from Screening occurred within 10 days of C1D1 unless the screening sample was unable to be processed or 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.

8 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). Subjects must continue to meet eligibility criteria on C1D1 pre-dose assessment in order to proceed with dosing.

9 Abiraterone combination only: ECHO or MUGA will be performed in screening and as clinically indicated once on study.

10 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).

11 Hematology evaluation must include hemoglobin, hematocrit, and white blood cell count with differential and platelet count. A complete list of required tests is found in Appendix 1 to the protocol.

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

13 Coagulation evaluation must include PT/INR, aPTT, fibrinogen, d-dimer, and Factor VII. A complete list of required tests is found in Appendix 1 to the protocol.

14 Subjects with a positive CTC sample at baseline, as indicated by a value of at least 5 cells/7.5 mL blood, will continue to have CTC samples collected while on treatment at each radiographic assessment timepoint. If the baseline sample does not meet this criterion then no additional CTC samples will be collected after the subject has received their first dose of PLX2853.

15 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.

16 On PK days, subjects should be instructed not to take their study drug dose (PLX2853, abiraterone acetate, and prednisone or PLX2853 and olaparib) at home.

17 Additional samples for PK may be collected if a subject experiences a DLT, serious adverse event, AE of special interest, or at the Sponsor's request. Samples for PK should be collected for any dose modification at predose and 0.5, 1, 2, 3, and 5 hours postdose (prior to second daily dose when applicable) 2 weeks (± 1 week) after the modification or at the next scheduled clinic visit if occurs no less than 1 week after the modification. The time since the last dose of PLX2853 and abiraterone acetate or PLX2853 and olaparib should be noted.

18

Assessment	**C1D1**	**C1D15**	**C2-4 D1**	**C2D15**	**C5+ D1**	**30-day FU**
ECG	Predose	Predose	Predose	Predose	Predose	Anytime
PK for PLX2853, abiraterone, and olaparib	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, 1 and 3 hours postdose	Predose, 1 and 3 hours postdose	Predose	Anytime
PD	Predose, 3 and 5 hours postdose	Predose, 3 hours postdose	Predose	N/A	Predose	Anytime

Note: All PK and PD samples and ECGs 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 and PD samples should be collected after the corresponding ECGs have been obtained.

19 Multiple pharmacodynamics 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).

20 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.

21 CT (or MRI for subjects with a contraindication to contrast) should include at minimum chest, abdomen, and pelvis. Soft tissue progression is assessed per RECIST v1.1 and does not require a confirmatory scan. Progression per bone scan is assessed per PCWG3 and requires a confirmatory bone scan at least 6 weeks later.

22 Radiographic assessment of tumor burden will occur every 9 weeks (±7 days) for the first 24 weeks of treatment (pre-C4, pre-C7, pre-C10), or more frequently as clinically indicated. After C10, radiographic assessments will occur every 12 weeks (pre-C14, pre-C18, etc.), or more frequently as clinically indicated. CTCs will be assessed at every radiographic assessment as indicated in footnote 14.

23 PLX2853 and abiraterone acetate should be taken at the same time. PLX2853 and the morning dose of olaparib should be taken at the same time. Subjects should fast for 2 hours before and 1 hour after taking the PLX2853 and abiraterone acetate or olaparib, except for PK collection days as noted above. The evening dose of olaparib may be taken with or without food. The tablets should be swallowed whole with water and not be crushed or chewed.

24 Prednisone should be taken at least 2 hours before PLX2853 and abiraterone acetate or 1 hour after taking PLX2853 and abiraterone acetate, except for PK collection days when subjects should take prednisone 1 hour after taking PLX2853 and abiraterone acetate.

25 Collection of completed drug diary and distribution of new diary to occur at the beginning of each cycle.

26 Subjects will be followed until death, withdrawal of consent, or loss to follow-up – every 3 months for the first 2 years 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.

27 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. Response assessment in follow up will include at minimum the modality used to determine response (radiographic imaging, PSA, and/or CTC assessment)

28 If the subject agrees to participate in the optional paired biopsy collection and the archival tissue provided was collected within 2 months of Screening, a fresh sample does not need to be collected at Screening for the optional paired biopsy sample. The paired biopsies should be from the same lesion if possible/feasible, and preferably from a non-target lesion.

29 Abiraterone and Prednisone Only: Subject must be receiving abiraterone acetate 1000 mg QD and prednisone 5–10 mg total daily dose at time of study entry.

30 Hemoglobin A1c evaluation is required within 28 days of C1D1 for all patients with confirmed or suspected Type 2 diabetes.

31 Serum testosterone evaluation is required within 28 days of C1D1 and all radiographic response timepoints while on study treatment (every 9 weeks for the first 24 weeks of treatment and then every 12 weeks).

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 2010). 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 (Filippakopoulos 2010; Nicodeme 2010) have since shown therapeutic effects in other solid tumors. 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 Metastatic Castration Resistant Prostate Cancer

1.3.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the second leading cause of cancer-related deaths in men in the United States. While treatment options are expanding, over 31,000 American men are still predicted to die from this disease in 2020 (Siegel 2019). The principal treatments for advanced prostate cancer are based on disrupting androgen receptor (AR) function, either by blocking production of androgens or by inhibiting androgen binding to its receptor. However, resistance to these treatments and disease progression is nearly universal. Patients who develop metastatic castration-resistant prostate cancer (mCRPC) generally succumb to the disease. Progression to mCRPC after androgen deprivation therapy (ADT) is driven by deregulated AR signaling (Taylor 2010; Chen 2004; Visakorpi 1995). Maintenance of AR signaling is the most common resistance mechanism that develops after conventional hormone treatments (Harris 2009). AR amplification, mutation or alternative splicing have all been identified as resistance mechanisms to anti-androgen treatments (Chen 2004; Taplin 1999; Sun 2010). Over one half of mCRPC patients have at least one of these aberrations in the AR pathway (Grasso 2012). Therapies that target AR signaling including abiraterone + prednisone (Stein 2012; Reid 2010; de Bono 2011) and enzalutamide (Mukherji 2012; Scher 2012) have become first-line therapies for mCRPC. Additionally, the PARP inhibitor, olaparib, has recently been approved for patients with HRR after progression on abiraterone or enzalutamide. As these are oral agents and generally well tolerated, they are favored over chemotherapy. Despite the success of AR signaling inhibitors and PARP inhibitors, durable responses are limited. All mCRPC patients will eventually progress despite evidence-based first-line treatments that patients receive. Additional agents with complementary mechanisms of action are required to help improve clinical outcomes.

1.3.2 Combination of BET Inhibitors with AR Signaling Inhibitors

Recent preclinical studies have shown that AR-signaling-competent human CRPC cell lines are preferentially sensitive to BET inhibitors (Asangani 2014). BRD4 physically interacts with the N-terminal domain of AR and can be disrupted by BET inhibitors such as JQ1 (Delmore 2011; Filippakopoulos 2010). Inhibiting the AR-BRD4 interaction disrupts transcription of AR target genes (Asangani 2014) and represents a promising strategy to block the function of AR in mCRPC resistance. BET inhibition by PLX2853 was found to be efficacious in CRPC xenograft mouse models such as VCaP model. This model is comprised of cells expressing both WT AR as well as the truncated variant ARv7 which can drive expression of AR target genes in the absence of androgen. Since BET inhibitors like PLX2853 can disrupt pathways downstream of AR by inhibiting multiple acetyl-lysine interactions, we have shown that PLX2853 in combination with abiraterone (EXP-20-AG9412) and enzalutamide (EXP-20-AH3303) can potentiate the

anti-androgenic effect as well as potentially overcome resistance to anti-androgenic therapies. This study will evaluate whether PLX2853 in combination with abiraterone + prednisone represents an effective approach for overcoming resistance to the approved therapy. Abiraterone + prednisone is selected based on the interim results from an ongoing randomized phase II study that favors abiraterone + prednisone over enzalutamide in patients with treatment-naïve mCRPC (Khalaf 2018).

1.3.3 Combination of BET Inhibitors with PARP Inhibitors

There is a unique subset of mCRPC patients with tumors harboring deleterious mutations in DNA-repair genes, in particular genes involved in homologous recombination repair (HRR). In these patients poly(ADP-ribose) polymerase (PARP) inhibitors have been reported to confer high rates of response. Recently, FDA has approved olaparib for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone acetate +prednisone. This represents an example of how mCRPC treatment can be tailored according to the tumor mutation profile. BET inhibitors have been shown to induce homologous recombination defects (HRD). This supports the evaluation of PLX2853 in combination with olaparib in mCRPC,

1.4 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, pharmacokinetics (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 solid tumor cancers. PLX2853 is currently in clinical development for both hematologic malignancies (Study PLX124-02 [NCT03787498]) and solid tumors (Studies PLX124-01 [NCT03297424] and PLX124-03 [NCT04493619]). The data to date have demonstrated evidence of antitumor activity with manageable toxicity. In clinical experience with PLX2853 monotherapy, at the time of protocol initiation, 2 evaluable subjects with heavily pretreated mCRPC were enrolled into a PLX2853 dose escalation study (PLX124-01; NCT03297424) with one subject having stable disease after 2 cycles of treatment before progressing after 4 cycles of treatment.

1.4.1 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 (Kd) values of PLX2853 were determined for the 8 isolated BET bromodomains. Based on the measured Kd 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 (inhibitory concentration $[IC]_{50}$ = 4.3 nM for BRD4 and 7.3 nM for BRD2) (EXP-16-AE6869).

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 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 CMV promoter and tandem repeats of a MYC binding element (E-box) to determine the cellular pharmacodynamic effect of PLX2853. PLX2853 potently inhibits MYC reporter activity in MV4-11 cells with an IC_{50} of 7.2 nM (EXP-16-AE6870).

The antitumor effects of PLX2853 were also evaluated in a panel of 127 solid tumor cell lines (EXP-15-AD8492), including five corresponding to prostate cancer cell lines (Table 2). Prostate cancer cell lines show sensitivity to PLX2853. This finding provides a rationale for testing PLX2853 as a potential new therapy in the treatment of prostate cancer.

Table 2: IC_{50} Values for PLX2853, Enzalutamide, and Niraparib in Prostate Cancer Cell Growth Assays

Cell Line	AR Status	BRCA Status	PLX2853 IC_{50} (µM) [CI_{95} (µM)]	Enzalutamide[a] IC_{50} (µM) [CI_{95} (µM)]	Niraparib[b] IC_{50} (µM) [CI_{95} (µM)]
DU145	AR negative	BRCA1/2 mutation	0.73 [0.596–0.895]	7.88 [N/A]	13.3 [12.6–14.1]
PC3	AR negative		0.655 [N/A]	>30 [N/A]	2.3 [N/A]
LNCaP	AR positive	BRCA2 mutation	0.00885 [0.00801–0.00978]	5.26 [3.4–8.14]	3.73 [3.22–4.32]
22Rv1	AR positive, full length and ARv7	BRCA2 mutation	0.0203 [0.0179–0.0229]	>30 [N/A]	2.56 [2.16–3.03]
VCaP	AR positive		0.00348 [0.00314–0.00385]	2.57 [1.23–5.4]	7.59 [5.8–10]

Source: EXP-20-AH3303

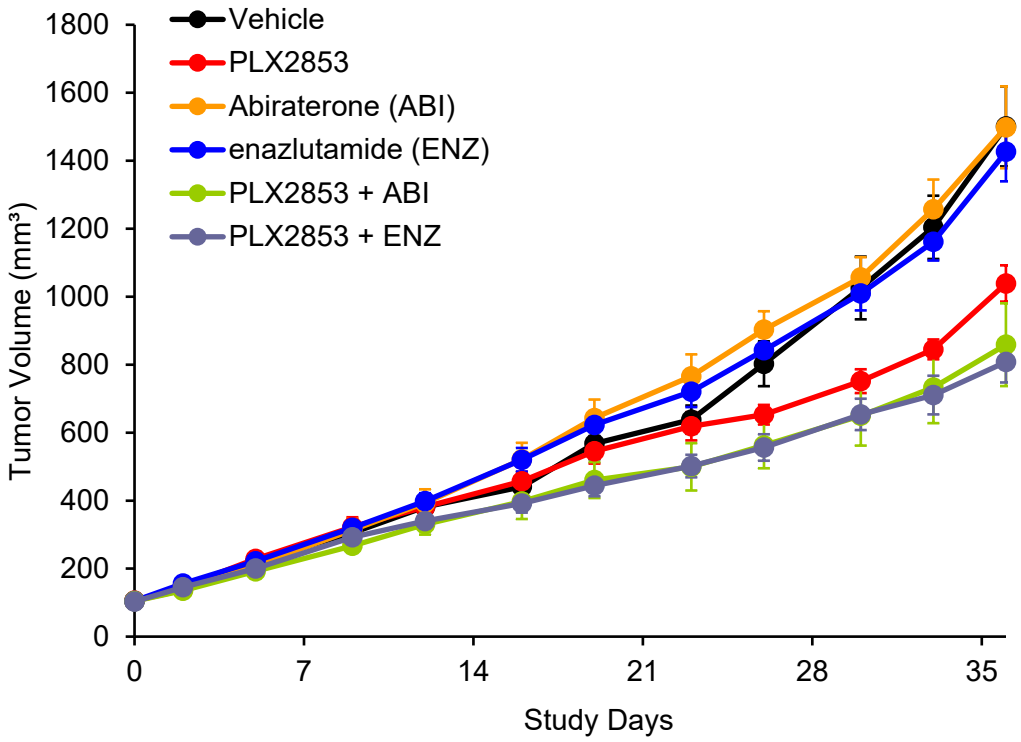
CI_{95} = 95% confidence interval; IC_{50} = Half maximal inhibitory concentration

[a] Enzalutamide was used as representative AR signaling inhibitor.

[b] Niraparib was used as representative PARP inhibitor.

Progression to mCRPC after ADT is primarily due to deregulated AR signaling. Initial treatments with agents such as abiraterone acetate and enzalutamide are successful but acquired resistance develops frequently. A number of paths leading to primary and acquired resistance to anti-androgen therapies have been reported. These include overexpression of androgen synthesis enzymes, amplification, and point mutations in AR, overexpression of the AR splice variant (ARv7), and induction of GR. BET inhibitors have been shown to avert these resistance mechanisms in vivo with mechanisms of action supported by extensive in vitro analyses (Vázquez 2019). In the xenograft model with 22Rv1 cell line, PLX2853 resensitizes both abiraterone and enzalutamide (Figure 1). We anticipate that combining PLX2853 with anti-androgen agents such as abiraterone acetate + prednisone and enzalutamide will result in more durable therapeutic responses in clinic.

Figure 1: PLX2853 in Combination with Abiraterone and Enzalutamide in the 22Rv1 Xenograft Model



Source: EXP-20-AG9412

BET inhibitors including PLX2853 have also been shown to induce homologous recombination defects (HRD) in cells which can render them sensitive to PARP inhibition. BET inhibitors and PARP inhibitors have shown strong synergy in tumor cells with germline or somatic mutations conferring a HRD state, resulting in improved efficacy in both in vitro and in vivo studies (Asangani 2014; Vázquez 2019). The ability of BET inhibitors to overcome resistance to PARP inhibition derives from their ability to induce HRD through down regulation of DNA-repair and damage response genes as well as other epigenetic modifications brought about by BET inhibition.

Together these data support two approaches: 1) the combination of PLX2853 with abiraterone acetate as a concerted blockade of AR signaling, the oncogenic driver in advanced CRPC; 2) potential for enhanced efficacy when combining PLX2853 with a non-AR-targeted therapy such as a PARP inhibitor (olaparib). Both strategies provide new possibilities to improve clinical outcomes for patients with advanced mCRPC.

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 solid tumors 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% tumor growth inhibition (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).

1.4.2 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 terminal elimination half-life ($T_{1/2}$) 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 time required to reach maximum observed concentration (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 a modest level of accumulation was observed at steady state. At the highest 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 liquid chromatography tandem mass spectrometry (LC/MS/MS) bioanalytical methods. Two GLP-compliant studies validated chromatographic methods used for quantification of PLX2853 in rat and dog plasma samples, as well as in aqueous media. The first method was performed using high performance liquid chromatography (HPLC) coupled with electro spray ionization in positive ion mode (ESI+) (LC/MS/MS) for rat and dog plasma sample analysis, and the second 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 oxidative 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,organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3 mediated transport in polarized monolayer of MDCK-II cells. PLX2853 demonstrated no potential to cause reversible and/or time-dependent inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. PLX2853 did not induce 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 crossover study where each group received a 40 mg 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 resulted in a significant reduction in exposure of PLX2853. The mean 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 CI_{90} for the ratios for C_{max}, and AUC_{0-24}, and area under the concentration-time curve from time zero extrapolated to infinite time ($AUC_{0-\infty}$) 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.

1.4.3 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 and in vivo 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 dogs 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 (EXP-16-AF1308)	*S. typhimurium*, *E. coli*	In vitro	≤5000 µg/plate
Chromosome aberration assay (EXP-16-AF1309)	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
Erythrocyte micronucleus assay and alkaline comet assay (EXP-20-AF1337)	Rat/Crl:CD (Sprague Dawley)	Oral (gavage)	5, 10, 20, 40
Other Toxicity Studies			
Phototoxicity assay (EXP-16-AF0914)	NIH/3T3 (ATCC® CRL-1658™)	In vitro	≤50 µM
Hepatocyte cytotoxicity assay (EXP-16-AF0943)	Human	In vitro	0.07–50.00 µM
Cell viability assay (EXP-16-AF0957)	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_{0-24} 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 PLX2853-treated cultures after 3 hours of treatment without metabolic activation. PLX2853 was also evaluated for its genotoxic potential in vivo in the bone marrow and liver of rats. In the micronucleus assay, increases in the incidence of micronucleated polychromatic erythrocytes (MnPCEs) were observed at ≥10 mg/kg. In the comet assay, no increases in % tail DNA were observed. Therefore, PLX2853 was positive for the induction of MnPCEs in rat bone marrow and negative for the induction of DNA damage in liver. The in vivo rat micronucleus assays results are consistent with the in vitro chromosomal aberration and indicate a potential for genotoxicity.

In a preliminary assessment of photosafety, 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.

1.4.4 Proposed Starting Dose for Study PLX124-04

The RP2D of 80 mg QD was determined in consideration of the totality of clinical, PD, and PK data across both advanced solid tumors and hematological malignancies. No DLTs were observed at or below 80 mg QD in Study PLX124-01 and Study PLX124-02 and in the safety lead-in of Study PLX124-03. An appropriate therapeutic index was observed at the RP2D with a sustained PD effect, and clinical efficacy was achieved across a broad range of malignancies at or below the RP2D.

Combination treatment with PLX2853 + abiraterone acetate + prednisone or PLX2853 + olaparib may have a different safety profile compared with PLX2853 single agent. To ensure adequate safety margin in the combination trial, a starting dose of 40 mg/day for PLX2853 is recommended. Based on the clinical PD results and preclinical experience, the proposed starting dose of 40 mg/day for PLX2853 with abiraterone acetate + prednisone or with olaparib combination therapy is expected to be pharmacologically active and reasonably safe.

1.5 Study Rationale

During the past 15 years, there has been significant scientific progress and investment in drug development for patients with mCRPC. This has resulted in the market approval of several lines of systemic therapies on grounds of pain palliation, minimizing disease adverse effects, and overall survival (OS) prolongation. However, the reported impact on OS in mCRPC patients from each of these individual agents is still modest, resulting in an addition of only a few months. It is necessary to explore new molecular understanding of castration resistance and complementary mechanisms of action to enhance current therapies and improve clinical outcomes.

BET inhibitors such as PLX2853 have shown efficacy preclinically in multiple tumor types, including CRPC (Asangani 2014; Faivre 2018; Welti 2018; Pawar 2019; Coleman 2019). The transcription factor drivers of CRPC progression, including AR, are critically dependent on BET family members such as BRD4. In particular, BET inhibition disrupted the composition and function of AR-occupied enhancers. BET inhibitors inhibited the activity of the AR splice

variant ARdv7 and ligand-binding domain gain-of-function mutations, F877L and L702H. BET inhibitors also inhibit the activities of important parallel transcription factor drivers of CRPC such as MYC. In vivo, BET inhibitors displayed potent antiproliferative activity in models of resistance to second generation antiandrogens represented by abiraterone and enzalutamide (EXP-20-AH3303).

BET inhibitors including PLX2853 have also been shown to induce homologous recombination (HR) defects in cells which can render them sensitive to PARP inhibition. PARP inhibition is a recently approved approach for targeting and treating tumors with deficiencies in DNA repair mechanisms. The PARP family of enzymes are required for the correct repair of DNA single strand breaks. Inhibition of PARP enzymes leads to an increase in DNA single strand breaks which then lead to increased double strand breaks during replication. Cells that have functional homologous recombination (HR) machinery can correct these double strand breaks during cell division. However, cells that contain defects in their HR machinery are incapable of repairing such breaks and will undergo apoptosis. PARP inhibitors olaparib and rucaparib have recently been approved for the treatment of mCRPC patients with suspected or deleterious germline or somatic mutations associated with homologous recombination repair (HRR) genes who have progressed on prior treatment with abiraterone acetate or enzalutamide. Hence, there is a rationale for the combination of PLX2853 and olaparib in the treatment of prostate cancer based on their complementary mechanisms of action.

This study will evaluate the investigational drug PLX2853 when given on a background of the approved drug abiraterone acetate + prednisone in patients with mCRPC. PLX2853 will also be evaluated when given on a background of the approved drug olaparib in mCRPC patients with germline or somatic mutations in HRR genes identified by FoundationOne CDx or BRACAnalysis CDx. These two parallel groups will provide an initial assessment of safety/tolerability and potential for pharmacokinetic (PK) interaction between the respective drugs. In the PLX2853-abiraterone acetate + prednisone combination, subjects with mCRPC who develop disease progression whilst currently receiving initial treatment with abiraterone acetate + prednisone will be studied. Subjects with deleterious or suspected deleterious germline or somatic HRR genes mutated mCRPC who have progressed following prior treatment with abiraterone acetate + prednisone or enzalutamide will be studied in the PLX2853-olaparib combination.

Abiraterone acetate was selected based on the interim results of an ongoing randomized Phase 2 clinical study comparing abiraterone acetate versus enzalutamide in patients with treatment-naïve mCRPC (Khalaf 2018). A PSA decline of more than 50% occurred in 34% of abiraterone acetate treated patients compared to 4% in the enzalutamide treated patients ($p < 0.001$) after a median follow-up of 22.3 months. Additionally, the median time to PSA progression on 2nd-line therapy was 2.7 versus 1.3 months (hazard ration [HR] 0.38, 95% CI 0.26–0.56) in favor of abiraterone acetate. Lastly, the median OS was not reached versus 24.3 months (HR 0.82, 95% CI 0.53–1.27) in favor of abiraterone acetate.

Olaparib was selected based on the PROfound study. The study was divided into two cohorts based on patient HRR status. Cohort A, patients with BRCA1/2 or ATM mutations, and Cohort B, patients based on 12 gene HRR signature excluding BRCA1/2 and ATM. A statistically significant improvement was demonstrated for olaparib compared to investigator's choice in Cohort A for rPFS with a median of 7.4 months vs. 3.6 months (HR 0.34; 95% CI: 0.25, 0.47; p <0.0001), for OS with a median of 19.1 months vs. 14.7 months (HR 0.69; 95% CI: 0.50, 0.97, p = 0.0175) and for ORR 33% vs 2% (p <0.0001). A statistically significant improvement for olaparib compared to investigator's choice was also demonstrated for rPFS in Cohort A+B, with a median of 5.8 months vs. 3.5 months (HR 0.49; 95% CI: 0.38, 0.63; p <0.0001).

1.6 Potential Risks and Benefits

This study is intended to evaluate safety, PK, tolerability, and preliminary efficacy of PLX2853 in combination with abiraterone acetate and PLX2853 in combination with olaparib. The identified risks of treatment with BET inhibitors from preclinical experience and other clinical development programs are hematologic toxicities, including thrombocytopenia, 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. Nonclinical genotoxicity studies with PLX2853 (in vitro chromosomal aberration and in vivo rat micronucleus assays) identified chromosomal abnormalities indicating a potential for genotoxicity. Potential benefits for qualifying subjects with mCRPC include the opportunity to receive an experimental treatment that may increase the probability of clinical response, extend the duration of response, survival and/or symptomatic improvement.

As of 30 June 2021, a total of 79 subjects have received PLX2853 monotherapy at doses ranging from 5 to 180 mg QD and 40 to 60 mg BID in Studies PLX124-01, PLX124-02, and PLX124-03. No treatment-related deaths have been reported. A total of 5 subjects have experienced DLTs, all with PLX2853 monotherapy. In PLX124-01, 3 DLTs were reported: 2 subjects experienced a DLT of Grade 4 thrombocytopenia at 120 mg QD. One of the thrombocytopenia events also had three treatment-related serious adverse events (SAEs) of embolism, ischemic stroke, and subarachnoid hemorrhage reported at the same time. One subject experienced Grade 3 fatigue, Grade 2 cheilitis, and Grade 2 nausea at 40 mg BID requiring a dose reduction in cycle 1, which is a DLT. In PLX124-02, 2 DLTs were reported: 1 event of Grade 3 hyperbilirubinemia at 140 mg QD and one event of Grade 3 blood bilirubin increased at 180 mg QD.

The most common adverse events (AEs) associated with PLX2853 monotherapy reported in >10% of subjects are nausea, fatigue, diarrhea, anorexia, dysgeusia, vomiting, anemia, hyperbilirubinemia/blood bilirubin increased, and thrombocytopenia/platelet count decreased. Less common side effects recorded in >5% to 10% of subjects associated with PLX2853 are dizziness, dry mouth, gastroesophageal reflux disease, and leukopenia/white blood cell count decreased, hyponatremia, increased aspartate aminotransferase (AST), hyperglycemia, abdominal distension, dyspnea, hypophosphatemia, hypertension, prolonged aPTT, headache, hypokalemia, lymphopenia/lymphocyte count decreased, epistaxis, and weight decreased.

As of 30 June 2021, a single fatal case of potential differentiation syndrome has been identified in a subject with relapsed acute myeloid leukemia treated with a bromodomain inhibitor (PLX51107) in a clinical study sponsored by Plexxikon. Thus, the treatment of hematological myeloid malignancies with PLX2853 carries a theoretical risk for differentiation syndrome. No events of differentiation syndrome were reported in study PLX124-02 (R/R AML and High-risk MDS). There is no known basis for this risk in solid tumors.

Refer to the Reference Safety Information section of the Investigator's Brochure and applicable labels for abiraterone acetate, prednisone, and/or olaparib, for additional safety information.

1.7 Previous Pharmacokinetics and Pharmacodynamics Experience

1.7.1 PLX2853 Clinical Pharmacokinetics

As of 30 June 2021, exposure to PLX2853 has been evaluated in 4 clinical studies: PLX124-01, PLX124-02, PLX124-03, and PLX124-04. PLX2853 has been administered as a single agent in 3 studies and in combination with carboplatin, abiraterone acetate, prednisone, and olaparib in 2 studies.

The PK of PLX2853 was evaluated in 46 subjects in PLX124-01 (solid tumors and lymphoma) at dose levels between 5 mg/day and 120 mg/day using once daily (QD) or twice daily (BID) dosing in the fasted state. The time to peak plasma concentration (T_{max}) was approximately 1 hour. Dose-dependent increases in exposures (C_{max} and AUC_{0-24}) were observed on both Day 1 and Day 15 (steady-state). PK data indicated that QD and BID of the same total daily dose resulted in similar daily exposures. There was no significant accumulation observed at steady-state, which is consistent with the short terminal half-life.

The PK of PLX2853 was evaluated in 21 subjects in PLX124-02 (R/R AML and High-Risk MDS) at dose levels between 20 mg/day and 180 mg/day using QD dosing in the fasted state. Comparable exposures were achieved in Study PLX124-02 and Study PLX124-01.

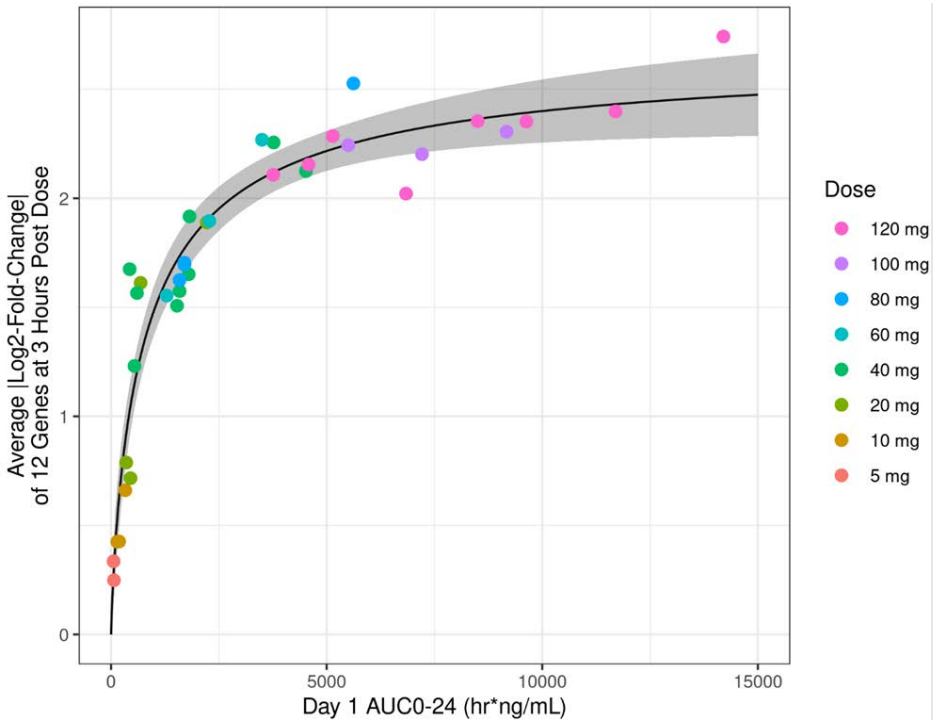
The PK of PLX2853 was evaluated in 17 subjects in PLX124-03 (advanced gynecological malignancies) at 80 mg QD monotherapy and at 40 mg QD and 80 mg QD in combination with carboplatin in the fasted state. Comparable exposures of PLX2853 were achieved in combination with carboplatin and as a single agent.

The PK of PLX2853 was evaluated in 3 subjects in PLX124-04 (mCRPC) at 40 mg QD in combination with abiraterone acetate and prednisone in the fasted state. Comparable exposures of PLX2853 were achieved in combination with abiraterone acetate and prednisone and as a single agent.

1.7.2 PLX2853 Clinical Pharmacodynamics

As of 30 June 2021, PD data were available from 36 subjects enrolled in Study PLX124-01. Analysis of peripheral blood cells from subjects 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 2 shows the dose response as measured by a 12-gene BET inhibitor responsive signature (the 12 genes are as follows: HEXIM1, WDR47, GLS, G3BP1, CALM1, CIRBP, CCR1, CCR2, TNFRSF8, SCIMP, BTN3A2, and KMO).

Figure 2: PLX2853 Pharmacodynamic Effect on Peripheral Blood Cells in Study PLX124-01 (Subjects with Solid Tumors)

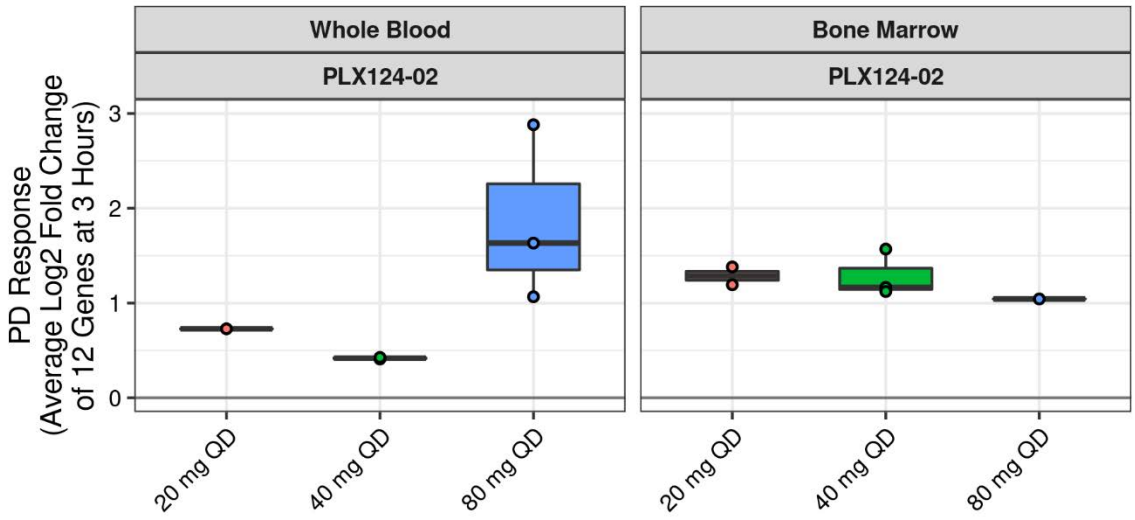


Of the 12 genes, 6 (HEXIM1, WDR47, GLS, G3BP1, CALM1, CIRBP) are up-regulated and 6 (CCR1, CCR2, TNFRSF8, SCIMP, BTN3A2, KMO) are down-regulated. The Y-axis shows the average of the absolute value of the Log2 fold change at 3 hours relative to baseline for the 12 genes. The figure above is plotted for Cycle 1 Day 1 data. The 40 and 60 mg dose levels include both once daily and twice daily dosing, where twice daily AUC_{0-24} was calculated as $2 \times AUC_{0-12}$.

Figure 3 shows the dose response as measured by a 12-gene BET inhibitor responsive signature in peripheral blood (Cycle 1 Day 1 [C1D1] 3 hours postdose versus C1D1 predose) and bone marrow (C2D1 3 hours postdose versus Screening) in PLX124-02 subjects. A robust PD

response in peripheral blood cells on C1D1 was measurable in all subjects at 3 hours postdose, with the highest responses observed at the 80 mg dose. Gene expression was also profiled in bone marrow aspirates that were collected at Screening and on C2D1, approximately 3 hours postdose. A consistent PD response was observed in the bone marrow cells of all 6 subjects on C2D1, but the magnitudes were not dose dependent.

Figure 3: PLX2853 Pharmacodynamic Effect in Peripheral Blood and Bone Marrow Cells in PLX124-02 (AML/MDS)



AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; QD = once daily

At the time of the cut-off, no PD data was available for PLX124-03 or PLX124-04.

2.0 STUDY OBJECTIVES

2.1 PLX2853 + Abiraterone Acetate + Prednisone Combination

2.1.1 Phase 1b (Dose Escalation)

The primary objective is as follows:

- To evaluate the safety and tolerability of PLX2853 + abiraterone acetate + prednisone including dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone

The secondary objective is as follows:

- To characterize the PK of PLX2853 and abiraterone and efficacy of PLX2853 combined with abiraterone acetate + prednisone in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone

2.1.2 Phase 2a (Dose Expansion)

The primary objective is as follows:

- To evaluate the efficacy of PLX2853 + abiraterone acetate + prednisone at the RP2D in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone

The secondary objective is as follows:

- To further characterize the safety and PK of PLX2853 and abiraterone when PLX2853 is combined with abiraterone acetate + prednisone in subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone

2.2 PLX2853 + Olaparib Combination

2.2.1 Phase 1b (Dose Escalation)

The primary objective is as follows:

- To evaluate the safety and tolerability of PLX2853 + olaparib including dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide

The secondary objective is as follows:

- To characterize the PK of PLX2853 and olaparib and efficacy of PLX2853 combined with olaparib in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide

2.2.2 Phase 2a (Dose Expansion)

The primary objective is as follows:

- To evaluate the efficacy of PLX2853 + olaparib at the RP2D in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide

The secondary objective is as follows:

- To further characterize the safety and PK of PLX2853 and olaparib when PLX2853 is combined with olaparib in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide

2.3 Exploratory Objectives (Both Phases, Both Combinations)

The exploratory objectives are as follows:

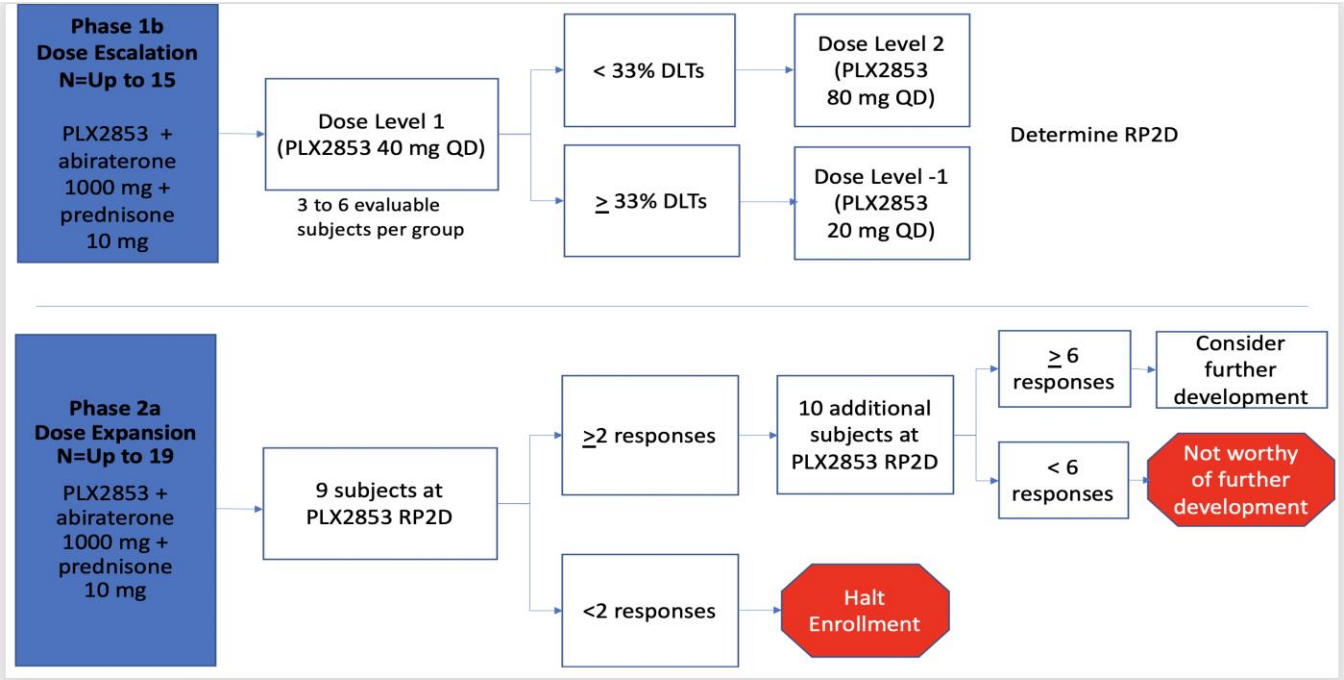
- To assess biomarkers in peripheral blood cells, tumor cells, and tissue biopsies
- To further evaluate the pharmacodynamics (PD) of PLX2853

3.0 STUDY DESIGN

3.1 PLX2853 + Abiraterone Acetate + Prednisone Combination Therapy

This multicenter, open-label, 2-part study will evaluate the safety, PK, PD, and efficacy of PLX2853 + abiraterone acetate + prednisone combination therapy in subjects with mCRPC who develop disease progression, while currently receiving initial abiraterone acetate and prednisone therapy, as documented by radiographic imaging, prostate-specific antigen (PSA), or clinical assessment. The study schema is presented in Figure 4.

Figure 4: Study Schema, PLX2853 + Abiraterone Acetate + Prednisone Combination Therapy



QD = once daily; RP2D = recommended Phase 2 dose

3.1.1 Phase 1b – Determination of RP2D of PLX2853 in Combination with Abiraterone Acetate and Prednisone

The safety, PK, PD, and efficacy of the combination of PLX2853 + abiraterone acetate + prednisone will be evaluated. The study population is patients with mCRPC who develop disease progression while currently receiving initial abiraterone acetate therapy, as documented by radiographic imaging, prostate-specific antigen (PSA), or clinical assessment. The combination of PLX2853 + abiraterone acetate + prednisone will be administered daily in 21-day treatment cycles. A standard "3+3" dose-escalation design will be followed. The starting dose level (Cohort 1) of PLX2853 will be 40 mg, which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day defined in study PLX124-01 (NCT03297424). PLX2853 will be administered once daily + abiraterone acetate 1000 mg orally once daily + prednisone 5 mg orally twice daily. Note

that the doses of abiraterone acetate and prednisone are fixed and will not be modified. See Section 5.4 for a full description of the dose escalation plan.

3.1.2 Phase 2a – Dose Expansion for Combination of PLX2853 + Abiraterone + Prednisone

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

Initially, 9 subjects will be enrolled to assess for efficacy in Phase 2a. If 2 or more responses are observed in the first 9 evaluable subjects, an additional 10 evaluable subjects will be enrolled. Subjects in Phase 2a who do not complete their 12-week disease response assessment for reasons other than toxicity or disease progression may be replaced.

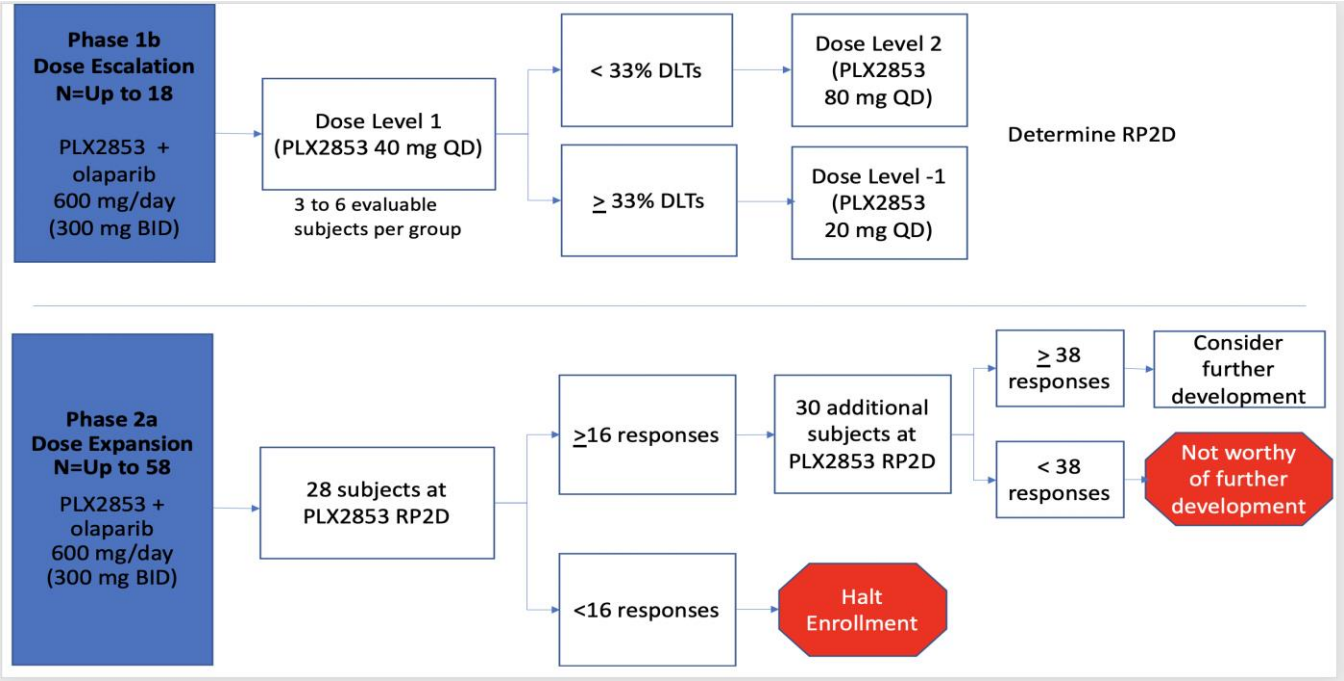
3.1.3 Pharmacokinetics of PLX2853 and Abiraterone

PLX2853 and abiraterone PK data will be analyzed in each dosing cohort for maximum observed concentration (C_{max}), AUC, and accumulation 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 of PLX2853 in combination with abiraterone acetate and prednisone may be studied, such as alternate-day dosing (e.g., every other day) depending on emerging safety and PK data for the combination.

3.2 PLX2853 + Olaparib Combination Therapy

This multicenter, open label 2-part study will evaluate the safety, PK, PD, and efficacy of PLX2853 + olaparib combination therapy in subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed, as documented by radiographic imaging, prostate-specific antigen (PSA), or clinical assessment, following prior treatment with abiraterone acetate and prednisone or with enzalutamide. This combination will only be investigated in regions where olaparib is approved. This combination will only be investigated in regions where olaparib is approved. The study schema is presented in Figure 5.

Figure 5: Study Schema, PLX2853 + Olaparib Combination Therapy



QD = once daily; RP2D = recommended Phase 2 dose

3.2.1 Phase 1b – PLX2853 + Olaparib

The safety, PK, PD, and efficacy of PLX2853 + olaparib will be evaluated. The study population is patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate and prednisone or with enzalutamide, as documented by radiographic imaging, prostate-specific antigen (PSA), or clinical assessment. This combination will only be investigated at U.S. sites. The combination of PLX2853 + olaparib will be administered daily in 21-day treatment cycles. A standard "3+3" dose-escalation design will be followed. The starting dose level (Cohort 1) of PLX2853 will be 40 mg, which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day defined in study PLX124-01 (NCT03297424). PLX2853 will be administered once daily + olaparib 600 mg (300 mg twice daily). Note that the dose of olaparib is fixed and will not be modified. See Section 5.4 for a full description of the dose escalation plan.

3.2.2 Phase 2a – Dose Expansion for Combination of PLX2853 + Olaparib

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

Initially, 28 subjects will be enrolled to assess for efficacy in Phase 2a. If 16 or more responses are observed in the first 28 evaluable subjects, an additional 30 evaluable subjects will be

enrolled. Subjects in Phase 2a who do not complete their 12-week disease response assessment for reasons other than toxicity or disease progression may be replaced.

3.2.3 Pharmacokinetics of PLX2853 and Olaparib

PLX2853 and olaparib PK data will be analyzed in each dosing cohort for C_{max}, AUC, and accumulation 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 of PLX2853 in combination with olaparib may be studied, such as alternate-day dosing (e.g., every other day) depending on emerging safety and PK data for the combination.

3.3 Number of Subjects

Up to 110 evaluable subjects will be enrolled.

PLX2853 + Abiraterone Acetate + Prednisone Combination

Phase 1b: Up to 15 evaluable subjects

- Approximately 9 to 15 evaluable subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone

Phase 2a (Dose Expansion): Up to 19 evaluable subjects

- There will be a single Simon's 2-stage design cohort of between 9 to 19 evaluable subjects with mCRPC who develop disease progression while currently receiving initial treatment with abiraterone acetate and prednisone

PLX2853 + Olaparib Combination

Phase 1b: Up to 18 evaluable subjects

- Approximately 9 to 18 evaluable subjects, with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate or enzalutamide.

Phase 2a (Dose Expansion): Up to 58 evaluable subjects

- There will be a single Simon's 2-stage design cohort of between 28 to 58 evaluable subjects with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with abiraterone acetate or enzalutamide

3.4 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 21-day cycles until subject discontinuation or withdrawal or study termination (see Section 7.1.5).
- **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:** Subjects will be followed until death, withdrawal of consent, or loss to follow-up according to the following schedule:
  - First two 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. Response assessment in follow up will include at minimum the modality used to determine response (radiographic imaging, PSA, and/or CTC assessment)

3.5 Endpoints

3.5.1 PLX2853 + Abiraterone Acetate + Prednisone Combination

3.5.1.1 Phase 1b – Primary Endpoint

Primary Endpoint:

- Incidence of DLTs, TEAEs, changes in safety parameters, and unacceptable toxicities

3.5.1.2 Phase 2a – Primary Endpoints

Primary Endpoints:

- Response as defined by any of the outcomes listed below. If any of these occur, the subject will be considered to have responded.
  - Objective response by per RECIST v1.1 with a minimum interval for confirmation of CR and PR of 4 weeks

- PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later
- Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline)

3.5.2 PLX2853 + Olaparib Combination

3.5.2.1 Phase 1b – Primary Endpoint

Primary Endpoint:

- Incidence of DLTs, TEAEs, changes in safety parameters, and unacceptable toxicities

3.5.2.2 Phase 2a – Primary Endpoint

Primary Endpoint:

- Response as defined by any of the outcomes listed below. If any of these occur, the subject will be considered to have responded.
  - Objective response by modified RECIST v1.1 with a minimum interval for confirmation of CR and PR of 4 weeks
  - PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later
  - Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline)

3.5.3 Both Phases, Both Combinations

3.5.3.1 Both Phases – Secondary Endpoints

Secondary Endpoints:

- Radiographic progression-free survival (rPFS)
- Time to PSA progression
- Duration of PSA response
- Overall survival defined as the time from the first dose of study drug to the date of death due to any cause
- Incidence of TEAEs, changes in safety parameters, and unacceptable toxicities

- PK parameters of PLX2853 and abiraterone and PLX2853 and olaparib following single and repeated dosing
- BOR per RECIST v1.1
- DOR (time from date of first documented, confirmed response using RECIST v1.1 and PCWG3 until date of documented progression or death from any cause).
- Time to first SSRE defined as:
  - Use of radiation therapy to prevent or relieve skeletal symptoms.
  - Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation is required.
  - Occurrence of spinal cord compression. Radiologic documentation required.
  - Orthopedic surgical intervention for bone metastasis.

3.5.3.2 Both Phases – Exploratory Endpoints

Exploratory Endpoints:

- Analysis of peripheral blood cells for dose- and exposure-dependent changes in the expression of BET target genes as measured by a 12-gene BET inhibitor responsive signature
- Pharmacodynamic assessments for potential biomarkers

3.6 Randomization

None of the subjects in this study will be randomized.

4.0 STUDY POPULATION

Subjects must meet the following inclusion and not meet the following exclusion criteria to be enrolled in the study.

4.1 Inclusion Criteria

Inclusion Criteria Applicable to Both Combinations:

1. Age ≥18 years at the time of signing informed consent.
2. Histologically confirmed adenocarcinoma of the prostate with tumor tissue available for molecular analyses.
3. Serum testosterone level of <50 ng/dL (<2.0 nM) assessed within 28 days of C1D1 and surgically or medically castrated and/or receiving treatment with an LHRH/GnRH analogue (agonist/antagonist).
4. Subjects must continue primary androgen deprivation with an LHRH/GnRH analogue (agonist/antagonist) or have received an orchiectomy. If receiving primary androgen deprivation therapy, this therapy must have been initiated at least 28 days prior to start of study dosing and must be continued throughout the study.
5. Eastern Cooperative Oncology Group Performance Status 0 to 1.
6. Adequate organ function as demonstrated by the following laboratory values. All Screening laboratory tests should be performed within 10 days prior to the first PLX2853 dose.
   - Hematological:
     - Neutrophils ≥1500/µL.
     - Platelets ≥100,000/µL (transfusion not permitted within 28 days prior to screening blood draw for olaparib, 14 days for abiraterone).
     - Hemoglobin ≥9 g/dL (transfusion and erythropoietin not permitted within 28 days prior to screening blood draw for olaparib, 14 days for abiraterone).
   - Renal:
     - Measured (by 24-hour urine collection) or calculated Creatinine Clearance (CrCL) >50 mL/min. The Cockcroft-Gault formula should be used for calculation (Appendix 1).
   - Hepatic:
     - Serum total bilirubin ≤1.5 × upper limit of normal (ULN).

       Exception for elevated bilirubin secondary to Gilbert's disease. 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 × ULN.

       For subjects with metastatic liver metastases ≤2.5 × ULN.

- Coagulation:
  - International normalized ratio (INR) ≤1.5 × ULN.
  - Activated partial thromboplastin time (aPTT) ≤1.5 × ULN.
- Chemistry:
  - Albumin ≥3.0 g/dL.

7. Fertile male subjects with female sexual partners must agree to use a highly effective method of birth control (defined in Section 4.2.1) during the study and for 90 days after the last dose of study drug.
8. Except as specified above for organ function, all drug-related toxicity from previous cancer therapy (including ongoing abiraterone acetate + prednisone therapy if applicable) must be resolved (to Grade ≤1 or baseline per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) prior to study treatment administration (Grade 2: alopecia, hot flashes, decreased libido, or neuropathy is allowed).
9. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

Inclusion Criteria Applicable to PLX2853 + Abiraterone Acetate + Prednisone Combination:

10. Currently receiving initial abiraterone acetate 1000 mg QD and prednisone per the abiraterone acetate label as most recent systemic therapy for mCRPC and showing evidence of progression as assessed by the investigator with one or more of the following (subjects who begin treatment in the hormone sensitive setting and progress to mCRPC and have not discontinued their initial abiraterone acetate treatment are not excluded). Subjects must be on a stable dose of prednisone for at least 14 days prior to C1D1:
    a. PSA progression defined, per PCWG3 criteria (Scher 2016; Appendix 6) at trial entry, as ≥2 occurrences of rising PSA levels with a minimum interval of 1 week and a PSA concentration of ≥1 ng/mL if confirmed PSA rise is the only measure of progression.
    b. Worsening measurable disease on CT/MRI per RECIST v1.1 criteria or at least one new documented bone lesion on a bone scan.
11. Potassium within normal limits.

Inclusion Criteria Applicable to PLX2853 + Olaparib Combination:

12. Prior genetic testing completed with known deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutation per FDA label for mCRPC as defined by an FDA-approved companion diagnostic (HRR mutation must be known prior to consent).
13. Prior treatment with abiraterone acetate and/or enzalutamide for metastatic prostate cancer and/or CRPC.
14. Evidence of radiographic progression of metastatic disease at study entry as assessed by the investigator defined as measurable disease on CT/MRI per RECIST v1.1 criteria or at least one documented bone lesion on a bone scan. Subjects whose disease spread is limited to regional pelvic lymph nodes or local recurrence (e.g., bladder, rectum) are not eligible.

4.2 Exclusion Criteria

Exclusion Criteria Applicable to Both Combinations:

1. Prior exposure to a bromodomain inhibitor.
2. Ongoing systemic infection requiring antibiotic, antiviral, or antifungal treatment.
3. History of 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. Symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable and asymptomatic.
6. Known or suspected allergy to the investigational agent or any agent given in association with this study.
7. 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 TdP can be found in Appendix 4.
   - QTcF ≥450 msec at Screening (based on average of triplicate 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 or left ventricular ejection fraction measurement of <50% at baseline. Subjects must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or have had a coronary artery bypass, angioplasty, vascular stent, or myocardial infarction within the past 6 months.
   - Uncontrolled hypertension, defined as systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg which 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).

8. 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.
9. Non-healing wound or ulcer.
10. 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.
11. 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. These subjects must be willing to undergo additional testing per local standard of care.
12. Baseline moderate or severe hepatic impairment (Child-Pugh Class B and C).
13. Active known second malignancy with the exception of any of the following:
    - Adequately treated basal cell carcinoma or squamous cell carcinoma of the skin.
    - 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.
14. Major surgery or significant traumatic injury within 28 days of Cycle 1 Day 1.
15. Currently receiving medications known to be strong or moderate inducers or inhibitors of CYP3A4 and substrates of CYP2D6 with a narrow therapeutic window (Appendix 2). These strong and moderate inducers, inhibitors and substrates must be discontinued at least 7 days prior to the first administration of study drug).
16. 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.
17. Any chronic medical condition requiring a dose of corticosteroids greater than 10 mg prednisone/prednisolone daily.
18. 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.

19. Subjects with a history of adrenal insufficiency, hyperaldosteronism, or pituitary dysfunction.
20. Poorly controlled known type 2 diabetes with HbA1C >7.5% (must be assessed within 28 days of C1D1 for any subject with known or suspected type 2 diabetes).
21. Live vaccine within 4 weeks of starting treatment.
22. Treatment with warfarin within 7 days of C1D1.
23. Subject is participating in any other therapeutic clinical study (observational or registry studies are allowed).
24. 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 in the study in the judgment of the Investigator.

Exclusion Criteria Applicable to PLX2853 + Abiraterone Acetate + Prednisone Combination:

25. Receipt of any anti-cancer therapy prior to Cycle 1 Day 1 with the exception of abiraterone acetate and GnRH therapy:
    - Prior systemic chemotherapy in the setting of mCRPC is not permitted (prior chemotherapy in the hormone-sensitive setting is allowed provided last dose was at least 6 months prior to Cycle 1 Day 1). Prior chemotherapy for any other disease within 2 years is prohibited.
    - Radiation therapy within 14 days prior to Cycle 1 Day 1.
    - Small molecule anti-cancer therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.
    - Immunotherapy 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) prior to Cycle 1 Day 1.
    - 5-α reductase inhibitors (e.g., finasteride, dutasteride), estrogen compounds (including estramustine) and megesterol are considered to be anti-cancer agents and prohibited within 21 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.

    Note: Subjects can receive a stable dose of bisphosphonates or denosumab for bone metastases before and during the study, as long as these were started at least 4 weeks prior to treatment with study drug.

Exclusion Criteria Applicable to PLX2853 + Olaparib Combination:

26. A medical history that includes any of myelodysplastic syndrome, monoclonal gammopathy of undetermined significance or acute myeloid leukemia.

27. Receipt of any anti-cancer therapy prior to Cycle 1 Day 1 with the exception of GnRH therapy:
    - Radiation therapy within 14 days prior to Cycle 1 Day 1.
    - Small molecule anti-cancer therapy for the treatment of cancer within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.
    - Immunotherapy 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) prior to Cycle 1 Day 1.
    - 5-α reductase inhibitors (e.g., finasteride, dutasteride), estrogen compounds (including estramustine) and megesterol are considered to be anti-cancer agents and prohibited within 21 days or 5 half-lives (whichever is shorter) prior to Cycle 1 Day 1.
    - Prior treatment with DNA-damaging cytotoxic chemotherapy (including platinum-based agents, cyclophosphamide, and mitoxantrone) is excluded with the exception of estramustine. Non-DNA-damaging chemotherapy (docetaxel, cabazetaxel, etc.) within 14 days or 5 half-lives (whichever is shorter) is excluded. Any chemotherapy not listed requires Medical Monitor review and approval to confirm eligibility.

    Note: Subjects can receive a stable dose of bisphosphonates or denosumab for bone metastases before and during the study as long as these were started at least 4 weeks prior to treatment with study drug.
28. Prior exposure to a PARP inhibitor.

4.2.1 Birth Control Methods

Fertile male subjects with female sexual partners must agree to use two forms of approved contraception (i.e., a highly effective method of hormonal/intrauterine contraception with a failure rate <1% per year and 1 additional barrier method) during the study to 90 days after the last dose of study drug according to the below list:

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

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

Subjects with a pregnant or breast-feeding partner should use barrier method contraception (condom plus spermicidal gel).

5.0 STUDY TREATMENTS

5.1 Investigational Product and Test Article Properties

5.1.1 PLX2853 (Investigational Product)

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 Abiraterone Acetate (Test Article)

Abiraterone acetate 500 mg film-coated tablets are formulated with colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, and sodium lauryl sulfate (ZYTIGA®). The film-coating contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Abiraterone acetate 250 mg uncoated tablets are formulated with colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

5.1.3 Prednisone (Test Article)

Prednisone tablets 5 mg may contain the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, D&C Yellow No.10, docusate sodium, FD&C Yellow No. 6, magnesium stearate and sodium benzoate.

An equivalent approved steroid may be used where applicable (prednisolone is acceptable; other equivalent agents must be approved by Plexxikon Medical Monitor).

5.1.4 Olaparib (Test Article)

Olaparib tablets are available in 2 strengths, 100 mg and 150 mg. Both tablet strengths contain the following inactive ingredients: copovidone, mannitol, colloidal silicon dioxide, and sodium stearyl fumarate. The tablets are coated using hyperomellose, PEG-400, titanium dioxide, ferric oxide, and ferrosoferric oxide only in the 150 mg tablet strength. Please refer to the LYNPARZA® label for additional information.

5.2 Study Drug Administration

5.2.1 PLX2853 Administration

PLX2853 is formulated as 20-mg strength tablets for oral use. Subjects should fast for 2 hours before and 1 hour after taking PLX2853 (See Section 5.2.3) Tablets will be taken orally with water. PLX2853 should be taken at approximately the same time each day. PLX2853 tablets

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) 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 21-day cycles. Guidance for dose modification is in Section 6.2.

5.2.2 Abiraterone Acetate Administration

Abiraterone acetate 1000 mg is administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone acetate (ZYTIGA® or generic equivalent) is available as either 500 mg film-coated tablets or 250 mg uncoated tablets. Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone acetate is taken and for at least 1 hour after the dose of abiraterone acetate is taken. The tablets should be swallowed whole with water and not be crushed or chewed. Please refer to the ZYTIGA® FDA label or SmPC for additional information.

PLX2853 and abiraterone acetate should be taken at the same time.

5.2.3 Prednisone Administration

Prednisone 5 mg tablets are administered per the label for abiraterone acetate. Prednisone is recommended to be taken with food or milk at least 2 hours before PLX2853 and abiraterone acetate or 1 hour after taking PLX2853 and abiraterone acetate, except for PK collection days when subjects should take prednisone with food or milk at least 1 hour after taking PLX2853 and abiraterone acetate. An equivalent approved steroid may be used where applicable (prednisolone is acceptable; other equivalent agents must be approved by the Plexxikon Medical Monitor).

5.2.4 Olaparib Administration

Olaparib 300 mg is administered orally twice daily. The morning dose of olaparib should be taken at the same time as PLX2853 and subjects should fast for at least 2 hours before and 1 hour after taking PLX2853 and olaparib. The evening olaparib dose may be taken with or without food. The tablets should be swallowed whole with water and not be chewed, crushed, dissolved, or divided. Please refer to the LYNPARZA® FDA label for additional information.

5.2.5 Dosing on PK Sample Collection Days

On PK sample collection days, subjects should be instructed *not* to take their morning dose of PLX2853, abiraterone acetate, and prednisone, or PLX2853 and olaparib at home before the clinic visit. The time of dosing will be recorded in the clinic. Subjects should fast at least 2 hours before dose administration and 1 hour after administration of PLX2853 and abiraterone acetate or PLX2853 and olaparib. On PK days, prednisone should be taken at least 1 hour after taking

PLX2853 and abiraterone. On non-PK sample collection days, the subject will take PLX2853 and abiraterone acetate or PLX2853 and olaparib at the same time independently, and (for abiraterone combo subjects) prednisone should be taken at least 2 hours before or 1 hour after taking PLX2853 and abiraterone acetate. Dosing information should be recorded in the study drug administration diary.

5.3 PLX2853 Dose Escalation

In Phase 1b dose escalation for both combinations, cohorts will be enrolled using a standard "3+3" design. The starting dose level of PLX2853 will be 40 mg administered orally once daily taken in combination with either abiraterone acetate 1000 mg administered orally once daily and prednisone 5 mg administered orally twice daily, or olaparib 300 mg administered orally twice daily. In the absence of a DLT in the first cycle of treatment and in conjunction with review of the PK and available pharmacodynamics data from each cohort by the Study Committee, dose escalation of PLX2853 is planned to occur in the following manner:

- DLTs will be assessed in the first treatment cycle.
- The starting dose of PLX2853 will be 40 mg/day (Cohort 1), which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day.
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be investigated. If that dose level is intolerable, the study will be halted.

5.4 Dose Escalation Plan

5.4.1 Dose Escalation Plan for the Combination of PLX2855 + Abiraterone Acetate + Prednisone

The combination of PLX2853 + abiraterone acetate + prednisone will be administered daily in 21-day treatment cycles. A standard "3+3" dose-escalation design will be followed. Three dose levels of PLX2853 are planned (Table 4). The starting dose level (Cohort 1) of PLX2853 will be 40 mg, which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day defined in study PLX124-01 (NCT03297424). PLX2853 will be administered once daily + abiraterone acetate 1000 mg orally once daily + prednisone 5 mg orally twice daily. Note that the starting doses of abiraterone acetate and prednisone are fixed and will not be modified.

Table 4: Provisional PLX2853 Dose Escalation Plan for the Combination of PLX2853 + Abiraterone Acetate + Prednisone

Provisional Dose Escalation Plan			
Dose Level	**PLX2853 Dose (mg/day)[a]**	**Abiraterone Acetate Dose (mg/day)[a]**	**Prednisone Dose (total mg/day)[b]**
-1	20	1000	10
1	40	1000	10
2	80	1000	10

[a] Once daily (QD) dosing schedule unless otherwise specified. Initial cohort will assess QD dosing. Subsequent cohorts may evaluate alternative dosing regimens as agreed to by the Study Committee.

[b] 5 mg twice daily (BID) dosing schedule.

DLTs will be assessed in the first 21-day treatment cycle. In the absence of a DLT and in conjunction with review of the safety, PK, and available PD data from each dose cohort by the Study Committee, dose escalations are planned to occur in the following manner:

- A minimum of 3 to 4 subjects will be initially enrolled in Dose Level 1 (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 subjects (or ≥33% of the cohort) at a dose level, the dose at which this occurs will be considered intolerable and the MTD to have been exceeded. The highest dose level at which 0 or 1 of 6 subjects experience a DLT will be declared the RP2D.
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be studied. If that dose level is intolerable, the study will be halted.
- At least 6 subjects must be evaluable at a given dose level in order to be considered an RP2D.
- An RP2D may be declared at a dose level without reaching an MTD if further dose escalation is deemed unwarranted.
- Any subject who misses more than 25% of doses in Cycle 1 (e.g., ≥ 6 doses of PLX2853 in 21 days) for reasons other than a treatment-related AE, or is withdrawn from the study prior to completing Cycle 1 for reasons other than a DLT, will not be DLT evaluable and additional subject(s) may be enrolled to provide adequate data for dose escalation decision making.

After dosing has been completed in each cohort, safety, PK data, and PD 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 PD (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 21 days. Once all ongoing subjects in a dose cohort have been treated for at least two 21-day 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 a Grade 3 or higher treatment-related toxicity and have completed 2 cycles of PLX2853. Any intra-subject dose escalation requires a discussion and agreement with the Medical Monitor.

5.4.2 Dose Escalation Plan for Combination of PLX2853 + Olaparib

The combination of PLX2853 + olaparib will be administered daily in 21-day treatment cycles. A standard "3+3" dose-escalation design will be followed. Three dose levels of PLX2853 are planned (Table 5). The starting dose level (Cohort 1) of PLX2853 will be 40 mg, which is 50% below the PLX2853 monotherapy RP2D of 80 mg/day defined in study PLX124-01 (NCT03297424). PLX2853 will be administered once daily + olaparib 600 mg once daily. Note that the starting dose of olaparib is fixed and will not be modified.

Table 5: Provisional Dose Escalation Plan for the Combination of PLX2853 + Olaparib

Provisional Dose Escalation Plan		
Dose Level	**PLX2853 Dose (mg/day)[a]**	**Olaparib Dose (total mg/day)[b]**
-1	20	600
1	40	600
2	80	600

[a] Once daily (QD) dosing schedule unless otherwise specified. Initial cohort will assess QD dosing. Subsequent cohorts may evaluate alternative dosing regimens as agreed to by the Study Committee.

[b] 300 mg twice daily (BID) dosing schedule.

DLTs will be assessed in the first 21-day treatment cycle. In the absence of a DLT and in conjunction with review of the safety, PK, and available PD data from each cohort by the Study Committee, dose escalation is planned to occur in the following manner:

- A minimum of 3 to 4 subjects will be initially enrolled in Dose Level 1 (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 subjects (or ≥33% of the cohort) at a dose level, the dose at which this occurs will be considered intolerable and the MTD to have been exceeded. The highest dose level at which 0 or 1 of 6 subjects experience a DLT will be declared the RP2D.
- If Dose Level 1 is not tolerated, Dose Level -1 (20 mg/day) will be studied. If that dose level is intolerable, the study will be halted.

- At least 6 subjects must be evaluable at a given dose level in order to be considered an RP2D.
- An RP2D may be declared at a dose level without reaching an MTD if further dose escalation is deemed unwarranted.
- Any subject who misses more than 25% of doses in Cycle 1 (e.g., ≥ 6 doses of PLX2853 in 21 days) for reasons other than a treatment-related AE, or is withdrawn from the study prior to completing Cycle 1 for reasons other than a DLT, will not be DLT evaluable and additional subject(s) may be enrolled to provide adequate data for dose escalation decision making.

After dosing has been completed in each cohort, safety, PK data, and PD 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 PD (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 21 days. Once all ongoing subjects in a dose cohort have been treated for at least two 21-day 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 a Grade 3 or higher treatment-related toxicity and have completed 2 cycles of PLX2853. Any intra-subject dose escalation requires a discussion and agreement with the Medical Monitor.

5.5 Concomitant Medications (and Procedures)

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. 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.

Dosing interruptions longer than 2 weeks should generally result in discontinuation from the study, unless the subject has demonstrated a clinical benefit (see Section 6.2). Consideration should be given to taper prednisone any time a dose hold is required for abiraterone acetate.

LHRH/GnRH Analogs

Subjects must have started treatment with an LHRH/GnRH analog at least 28 days prior to first dose and must continue treatment while on study or should have had a bilateral orchiectomy.

Inhibitors and Inducers of CYP

Because the rate of metabolism of PLX2853 is very low, CYP2C8 and CYP3A4 inhibitors are not expected to have a significant effect on the clearance of PLX2853. However, in the event they alter the systemic exposure to PLX2853, strong inhibitors or inducers of CYP3A4 and CYP2C8 should be avoided unless necessary and after discussion with the Medical Monitor (see Appendix 2 for a list of strong CYP3A4/2C8 inhibitors and inducers). Abiraterone acetate is an inhibitor of CYP2C8 and may affect plasma levels of PLX2853. Exposure will be monitored for both PLX2853 and abiraterone.

In addition to the criteria specified above, the following criteria should be followed as applicable:

For subjects receiving abiraterone acetate: Co-administration with a strong CYP3A4 inducer or CYP2D6 substrate with a narrow therapeutic index are prohibited. If an alternative treatment cannot be used, PLX2853 and abiraterone acetate must be held until the strong CYP3A4 inducer or CYP2D6 substrate with a narrow therapeutic index is discontinued (see Appendix 2). Please refer to the ZYTIGA® label or SmPC for additional information.

For subjects receiving olaparib: strong and moderate CYP3A inhibitors and inducers should be avoided. Co-administration with strong or moderate CYP3A inhibitors should be avoided unless necessary. If a CYP3A4 inhibitor cannot be avoided, administration after discussion with the Medical Monitor and per the dose modification requirements specified in the label. Please refer to the LYNPARZA® label for additional information.

Antiemetics/Anti-Reflux Medications

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).

Proton pump inhibitors and other gastric pH modifiers should be avoided except for locally acting antacids, which can be administered 2 hours before or after PLX2853 administration.

Radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony 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. Study treatment should be restarted within 21 days as long as any bone marrow toxicity has recovered.

Bisphosphates and Denosumab

Subjects are permitted to continue treatment with bisphosphonates or denosumab if receiving a stable dose at least 4 weeks from starting study treatment. Once on study treatment, initiation of new bisphosphonate or denosumab therapy is not permitted, unless approved by the Medical Monitor. Dose adjustments may be allowed only after agreement between the Principal Investigator and Medical Monitor.

Anticoagulation Therapy

Treatment with warfarin is prohibited while on study treatment. In the event initiation of treatment with warfarin is clinically required, the subject must be discontinued from the study.

Biotin and Biotin-Containing Supplements

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.

Concomitant medications known to prolong the QT interval 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 Follow-up procedures are performed or until the initiation of a non-protocol therapy for the underlying malignancy, whichever occurs first.

5.6 Precautions and Restrictions

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

5.7 Management of Clinical Events

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

5.8 Blinding and Unblinding

Blinding methods will not be employed; PLX2853, abiraterone acetate, prednisone, and olaparib will be administered in open-label fashion.

5.9 Preparation, Reconstitution, and Dispensation

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

Refer to the applicable product labels for instructions on preparation, reconstitution, and dispensation for abiraterone acetate and prednisone (or equivalent) or olaparib.

5.10 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
11011 Torreyana Road #100
San Diego, CA 92121

Abiraterone acetate, prednisone (or equivalent), and olaparib will not be provided by the Sponsor and commercially available product should be used. They are packaged per their labels.

5.11 Storage, Handling, and Accountability

PLX2853 tablets, abiraterone acetate tablets, prednisone tablets, and olaparib 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, abiraterone acetate, prednisone, and/or olaparib at the recommended storage conditions noted on 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.

Refer to the Pharmacy Manual for additional details on accountability of all study drug, and storage and handling of PLX2853. Refer to the applicable product label for additional details on storage and handling of abiraterone acetate, prednisone, and olaparib (or equivalent).

5.12 Other Protocol-specified Materials

Central laboratory kits will be provided for sample collection, shipment, and storage for PK and pharmacodynamic 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 (21 days) of study drug administration that are *at least possibly related* to any study drug (PLX2853, abiraterone acetate, olaparib, or prednisone), and that meet one of the following CTCAE v5.0 criteria below. DLTs will be evaluated for each cohort. DLTs will be assessed during a DLT assessment window of 21 days in Cycle 1. Toxicities occurring in treatment Cycle 2 or later will be reviewed and their impact on dose escalation and dosing frequency assessed. If during the DLT window a subject requires treatment with a concomitant medication that results in a dose reduction of abiraterone acetate or olaparib (per their label), the patient will be considered inevaluable, unless the AE requiring treatment meets the definition of a DLT.

In Phase 1, a subject who misses greater than 25% of their expected doses in Cycle 1, or does not complete Cycle 1,for reasons other than a related toxicity will be considered inevaluable and may be replaced.

DLTs will be determined based on the following criteria:

Hematologic Toxicities

- Grade 4 neutropenia lasting >5 days
- Febrile neutropenia
- Grade 4 thrombocytopenia of any duration
- Grade ≥3 thrombocytopenia with clinically significant hemorrhage for any duration
- Grade 4 anemia

Non-Hematologic Toxicities

- A dose reduction required during Cycle 1 due to an AE (except as specified above)
- AE related treatment delays causing a subject to miss at least 25% of their total expected doses of any drug in the combination during Cycle 1
- Any Grade ≥3 non-hematologic toxicity of any duration, except:
  - Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours
  - Grade 3 fatigue lasting <5 days
  - Grade 3 hypertension that can be controlled with medical therapy
  - An increase of indirect (unconjugated) bilirubin indicative of M. Meulengracht/Gilbert's syndrome

  - Serum lipase and/or serum amylase Grade 3 ≤ 7 consecutive days without clinical signs or symptoms of pancreatitis
  - Grade 3 AST/ALT for <5 days
  - Grade 3 neuropathy in subjects with pre-existing Grade 2 neuropathy
- ALT/AST >3 x ULN with total bilirubin >2 x ULN without another explanation (e.g., cholestasis)
- Any Grade 3 clinically significant electrolyte imbalance confirmed with repeat assessment within 24 hours.

A subject who experiences a DLT may remain in the study and continue receiving PLX2853, abiraterone acetate, and prednisone or PLX2853 and olaparib 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 agreement by the Medical Monitor. If a subject is required to permanently discontinue at least one of the study medications for any reason they will be discontinued from all study treatment. For patients receiving abiraterone acetate, if PLX2853 and abiraterone acetate are withheld, then consideration should be given to tapering the dose of prednisone as clinically indicated.

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 (e.g., AEs meeting the criteria of a DLT occurring in Cycle 2 or later) are observed requiring dose reductions, dose escalation may be halted and more subjects may be treated at that or a lower dose level.

6.2 Dose Modification Guidelines

Reduction/interruption of dosing may take place for study drug-related AEs at any time. Table 6 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 or interruptions of abiraterone acetate, prednisone, or olaparib should follow their label, as well as the guidance below. If an AE requiring a dose modification of abiraterone acetate, prednisone, or olaparib is also at least possibly related to PLX2853, then PLX2853 should also be reduced by 1 dose level.

If 1 study drug needs to be temporarily held due to an AE, then all drugs should be held until the AE resolves per the dose modification guidelines, unless agreed upon by the investigator and Medical Monitor. If 1 study drug needs to be permanently discontinued, then all study drugs must be permanently discontinued. If abiraterone acetate is held/discontinued, consideration should be given to tapering the dose of prednisone as clinically indicated.

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. Every attempt should be made to keep to the 21-day cycle.

Dosing interruptions longer than 2 weeks due to a treatment-related AE should generally result in discontinuation from study treatment, 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.

In Cycle 2 and beyond, dose interruptions for Grade ≤2 non-hematologic toxicity can be implemented at the discretion of the treating physician to manage clinically significant toxicities. No dose reduction is required if treatment is resumed within 7 days. Discussion with Medical Monitor is required for holds lasting longer than 7 days.

For subjects being treated with abiraterone acetate and prednisone, monitor patients for hypertension, hypokalemia, and fluid retention. Control hypertension and correct hypokalemia before and during treatment. Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. Monitor for symptoms and signs of adrenocortical insufficiency, and consider increased dosage of corticosteroids before, during and after stressful situations. Monitor liver function and modify, interrupt, or discontinue dosing of abiraterone acetate as clinically indicated and per FDA label.

For subjects being treated with olaparib, if new or worsening pulmonary symptoms (e.g., dyspnea, cough and fever) or radiological abnormalities occur in the absence of a clear diagnosis, olaparib must be interrupted and further diagnostic workup (including a high resolution CT scan) should be performed promptly to assess the source of symptoms and exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be resumed at the same dose, if deemed appropriate by the investigator in consultation with the Medical Monitor. If pneumonitis is confirmed, discontinue olaparib and treat the subject appropriately.

Table 6: 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 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, resume at same dose.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until ANC recovers to ≥1 × 10^9/L; growth factor support permitted	If recovered to ANC ≥1 × 10^9/L in ≤7 days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	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 × 10^9/L and T ≤38°C in ≤7days, reduce dose by 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
	2nd Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC ≥1 × 10^9/L and T ≤38°C, reduce dose by an additional 1 dose level.
			If not recovered to ANC ≥1 × 10^9/L after 7 days, discontinue permanently.
	3rd Appearance	Discontinue permanently; provide growth factor support	N/A
Grade 3 or 4 thrombocytopenia without bleeding	1st Appearance	Interrupt until PLT ≥75 × 10^9/L	If recovered to PLT ≥75 × 10^9/L ≤7 days, resume at same dose.
			If not recovered to PLT ≥75 × 10^9/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance 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
Grade 3 anemia	Any Appearance	If transfusion support given: no dose hold required	N/A
		If no transfusion support given: Interrupt until resolved (Grade 0–1 or baseline)	Resume at same dose once recovered
Other Grade 3 toxicities (excluding transaminase increases, electrolyte imbalances, nausea, vomiting, diarrhea, anorexia, dehydration, fatigue, hypertension, and anemia)	1st Appearance	Interrupt until resolved (Grade 0–1 or baseline); start symptomatic treatment if possible	Reduce dose by 1 dose level
	2nd Appearance	Interrupt until resolved (Grade 0–1 or baseline); start symptomatic treatment if possible	Reduce dose by 1 dose level
	3rd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Grade 3 electrolyte imbalances, nausea, vomiting, diarrhea, anorexia, dehydration, fatigue, and hypertension	1st Appearance	Interrupt until resolved (Grade 0–1 or baseline; for hypertension only: asymptomatic Grade 2 with blood pressure <140/90 mm Hg is acceptable); start symptomatic treatment if possible	If recovered ≤5 days, resume at same dose.
			If symptoms persist for >5 days despite optimum treatment, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until resolved (Grade 0–1 or baseline; for hypertension only: asymptomatic Grade 2 with blood pressure <140/90 mm Hg is acceptable); start symptomatic treatment if possible	If recovered ≤5 days, reduce dose by 1 dose level.
			If symptoms persist for >5 days despite optimum treatment, discontinue permanently.
	3rd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A

PLX2853-Related Toxicities	Frequency	When to Hold or Stop	Dose Adjustments for Resumption[a]
Other Grade 4 toxicities (excluding transaminase increases, electrolyte imbalances, vomiting, and diarrhea)	1st Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Grade 4 electrolyte imbalances	1st Appearance	Interrupt until resolved (Grade 0–1 or baseline); start symptomatic treatment if possible	If recovered ≤2 days on optimum treatment, reduce dose by 1 dose level.
			If symptoms persist for >2 days despite optimum treatment, discontinue permanently.
	2nd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Grade 4 vomiting and diarrhea	1st Appearance	Interrupt until resolved (Grade 0–1 or baseline); start symptomatic treatment if possible	If recovered ≤5 days on optimum treatment, reduce by dose 1 dose level.
			If symptoms persist for >5 days despite optimum treatment, discontinue permanently.
	2nd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Transaminase increases	• ALT or AST >8 × ULN but <20 x 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 reduced dose.

PLX2853-Related Toxicities	Frequency	When to Hold or Stop	Dose Adjustments for Resumption[a]
	• Hy's Law: AST/ALT >3x ULN and total bilirubin >2 x ULN and ALP <2x 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	First appearance	Interrupt study drug until resolved.	Upon recovery to QTcF ≤500 msec (Grade ≤2), restart at a reduced dose. Permanently discontinue study drug if the QTcF interval remains >500 msec and increased >60 msec from pretreatment values (after controlling cardiac risk factors for QT prolongation, e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias).[b]

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECG = electrocardiogram; INR = International Normalized Ratio; N/A = not applicable; PLT = platelet; ULN = upper limit of normal

[a] See Table 4 for PLX2853 + abiraterone and prednisone dose levels. See Table 5 for PLX2853 + olaparib dose levels.

[b] QTcF : Only 1 dose reduction is permitted per subject. Prior to and following treatment initiation or after dose modification of study drugs for QTcF 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 7. 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 Investigational Site File Binder. A full list of investigators is available in the Sponsor's investigator database.

Table 7: Contact Information

Medical Monitor: (Emergency Contacts)	Jackie Walling, MBChB, PH.D Vice President, Clinical Development Plexxikon Inc. 329 Oyster Point Blvd. South San Francisco, CA 94080, USA Phone: +1-650-483-9726 Fax: +1-510-548-8014 E-mail: jwalling@plexxikon.com
SAE Reporting Contact	Report all SAEs, whether related or not to study drug, by emailing a completed SAE form within 24 hours 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 dose escalation decisions and approximately monthly during the Phase 2a 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. The Study Committee charter will be provided as a separate document.

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

Subjects will be assigned sequentially to the dose cohort and phase of the study.

7.1.5 Withdrawal of Subjects from Drug Treatment and Study, and 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.

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 in Phase 1b who discontinue PLX2853 or abiraterone acetate/prednisone, or olaparib in Cycle 1, or miss greater 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. Study drug administration may be discontinued for an AE or at the discretion of the Investigator.

Subjects in Phase 2a who do not complete their 9-week disease response assessment for reasons other than disease progression may be replaced.

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, abiraterone acetate, prednisone, and olaparib 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 for Phase 1b 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, if applicable. A subject will be considered enrolled once they have received their first dose of PLX2853.

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 Investigational Site File Binder.

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.

7.2 Study Assessments

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 and Synopsis Table 2).

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).

Subjects will be followed every 3 months for the first 2 years after the 30-day FU visit and every 6 months for the third year after the 30-day FU period until death, withdrawal of consent, or loss to follow-up. 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 who discontinue study treatment without documented disease progression should have their disease monitored by radiographic imaging per standard of care until disease progression or starting any new anti-cancer therapy, whichever occurs first. Refer to the Schedule of Events (Synopsis Table 1 and Synopsis Table 2).

7.2.1 Disease Assessment

Radiographic Assessments will occur every 9 weeks for the first 24 weeks (pre-C4, pre-C7, pre-C10) and then every 12 weeks after (pre-C14, pre-C18, etc.), or more frequently as clinically indicated. Redacted copies of pathology, molecular pathology, and radiology reports should be sent to the Sponsor as part of the enrollment packet and may be requested after each tumor response assessment. In addition, redacted copies of radiology scans should be available for an independent review if requested by the Sponsor.

A subject will be considered to have disease progression if one or more of the following occurs:

- Progression by RECIST v1.1 - increase in measurable lesion size(s) or new lesion (Appendix 3)
- Progression by bone scan per PCWG3 with a confirmatory scan ≥ 6 weeks later
- PSA progression (defined per PCWG3 as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, which is confirmed by a second consecutive value obtained 3 or more weeks later). PSA progression alone does not necessitate treatment discontinuation.

Table 8: Radiographic Progression Criteria

Visit Date	Criteria for Bone Progression	Criteria for Soft Tissue Progression
Week 9	• 2 or more new lesions compared to baseline bone scan.	• Progressive disease on CT or MRI by RECIST v1.1
	• Requires confirmation scan at least 6 weeks later with > 2 additional lesions compared to week 9 scan	• No confirmation scan required.
Week 18 or later	• 2 or more new lesions compared to week 9 bone scan.	• Progressive disease on CT or MRI by RECIST v1.1
	• Requires confirmation scan at least 6 weeks later for persistence or increase in number of lesions	• No confirmation scan required.

7.2.1.1 Soft Tissue Evaluation

The imaging modalities used for RECIST v1.1 assessment will be CT or MRI scans of the chest, abdomen, and pelvis. Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of individual subjects. At assessments subsequent to baseline, any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumor burden used at baseline must be used at each subsequent assessment. Bone lesions will not be included in the RECIST v1.1 soft tissue assessment.

7.2.1.2 Bone Metastasis Evaluation

Bone lesions will be assessed by bone scintigraphy commonly performed with Technetium-99 (bone scans) based on PCWG3 criteria. Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment. Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions.

The first bone scan should be performed 9 weeks after initiating treatment unless clinically indicated, as there may be evidence of a flare response early on which may confuse the response evaluation. A patient will be considered to have progressed based on the criteria in Table 8.

7.2.1.3 PSA Evaluation

PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, which is confirmed by a second consecutive value obtained three or more weeks later (per PCWG3). Per PCWG3, in the event a subject meets the criteria for PSA progression <12 weeks after starting treatment, the subject should continue on treatment until documented PSA progression is confirmed ≥12 weeks from start of treatment or there is other evidence of disease progression prior to 12 weeks.

7.2.1.4 Symptomatic Skeletal-Related Events (SSRE)

SSREs will be assessed at each visit during the treatment phase, up to and including the study treatment discontinued visit. An SSRE is defined as one or more of the following:

- Use of radiation therapy to bone in order to prevent or relieve skeletal complications
- Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma)
- Occurrence of spinal cord compression
- A tumor related orthopedic surgical intervention.

The occurrence of a SSRE alone, in the absence of disease progression, does not necessitate treatment discontinuation.

7.2.2 Archival Tissue

Archival tissue samples will be collected at Screening. All subjects will be required to permit exploratory evaluations of their archival tumor tissue. If >6 months (approximately) have elapsed since the last biopsy, a repeat biopsy of representative lesions (in the judgment of the Investigator) is recommended, but not required. When available, tumor samples from soft tissue lesions should be submitted instead of tissue from bony metastatic sites. If bony tissue must be submitted, it cannot have been decalcified.

Refer to the Laboratory Manual for specific details on the archival tissue sample requirements.

7.2.3 Fresh Tumor Biopsy

Subjects with biopsy-accessible tumors will be asked to participate in an exploratory evaluation of paired biopsies, with samples taken at Screening, Cycle 2 Day 1, and any other time per the discretion of the Investigator. If the subject consents to the optional paired biopsies and 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.

7.2.4 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 and abiraterone acetate or PLX2853 and olaparib dose at home on PK or pharmacodynamics collection days.

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.

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 and Synopsis Table 2) within 2 weeks of the modification or at the next scheduled clinic visit, whichever occurs closes to the new dosing regimen. Additional samples for PK may also be collected if a subject experiences a DLT, SAE, adverse event of special interest (AESI), or at the Sponsor's request. A list of protocol-required PK and pharmacodynamics assessments is provided in Appendix 1.

A total volume of blood collected in Cycle 1 (21-day cycle) will be approximately 250 mL and all subsequent cycles will be no more than approximately 120 mL. Further information may be found in the Laboratory Manual.

7.2.5 Pharmacokinetic Assessments

The PK parameters of PLX2853 and abiraterone, or olaparib will be assessed by measuring the AUC from time zero to time of last measurable concentration postdose ($AUC_{0\text{-}last}$), AUC from time zero to 24 hours postdose ($AUC_{0\text{-}24}$), 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, $AUC_{0\text{-}last}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate.

7.2.6 Biomarker Samples and Pharmacogenomics

Baseline subject blood samples (serum, plasma, whole blood) will be obtained for pharmacodynamics and biomarker assessments. These may be repeated at subsequent time points throughout the study. In addition, subjects will be asked to submit archival tumor samples, and may be asked to have subsequent tumor biopsies while on the study. These tumor samples may be used for pharmacodynamics 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.

Pharmacodynamics 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:

- Gene expression, nucleic acid sequencing, histochemical and/or protein analyses of plasma, peripheral blood cells, and/or tumor tissue
- Analysis of CTC status and possibly other exploratory markers of response or resistance.

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

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.

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. Sample collection, preparation, handling, storage, and shipping instructions are in the Laboratory Manual. Blood volume for blood draws is provided in Section 7.3.

7.2.7 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), electrocardiogram (ECG), weight, ECOG, and vital signs.

7.2.7.1 Medical and Medication History

Medical history includes clinically significant diseases, ongoing symptoms, 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.

7.2.7.2 ECOG Performance Status Assessment

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

7.2.7.3 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.

7.2.7.4 Vital Signs

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

7.2.7.5 Height and Weight

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

7.2.7.6 Electrocardiogram

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

Triplicate ECGs should be done predose for 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.

7.2.7.7 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 (CS) or not clinically significant (NCS). 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.

7.3 Blood Collection

The estimated volumes of blood to be collected at each visit of the study are shown in Table 9 and Table 10. The quantities of blood are within accepted limits of 10.5 mL/kg or 550 mL (whichever is smaller) per NIH and other published guidelines (DF/HCC 2012; NIHCC 2009; NS LIJ 2013).

Table 9: Phase 1b: Approximate Blood Sample Volumes Collected

TEST▼	**Blood Sample Volumes (mL)**									
	SCR	**C1**				**C2**		**C3**	**C4+**	
STUDY DAY►	**D–28 to D-1**	**D1**	**D2**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**30-day FU**
WINDOW (days)►				**± 2**	**± 2**	**± 3**	**± 3**	**± 5**	**± 5**	**± 7**
PG blood sample	6									
Hematology[a]	8	8		8	8	8	8	8	8	8
Chemistry[a]	8	8		8	8	8	8	8	8	8
Coagulation tests[a]	8	8		8	8	8	8	8	8	8
CRP[a]	5	5		5	5	5		5	5	5
CTCs[b]		20							20[b]	20
PSA	10	10				10		10	10	10
HIV and Hepatitis A/B/C tests	9									
Pharmacodynamics blood samples		48.5[c]	2.5		5	31		31	31	31
PK blood samples		36	6		36	18	18	18	18	6
TOTAL VOLUME	**54**	**143.5[c]**	**8.5**	**29**	**70**	**88**	**42**	**88**	**88–108[d]**	**96**

30-day FU = 30-day follow-up visit; CRP = c-reactive protein; CTCs = Circulating Tumor Cells; PG = pharmacogenomics; PK = pharmacokinetic; SCR = Screening

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

[b] CTCs assessed (if at least 5 cells/7.5 mL blood detected at baseline) every 9 weeks (± 7 days) for the first 24 weeks of treatment (pre-C4, pre-C7, pre-C10), then every 12 weeks after (pre-C14, pre-C18, etc.), or more frequently as clinically indicated.

[c] Subjects receiving abiraterone, an extra 10 mL of blood drawn for ARv7 testing on C1D1 (further details are in laboratory manual). Subjects receiving olaparib will have an estimated 38.5 mL of PD pharmacodynamics blood samples (121.5 mL total) drawn on C1D1.

[d] Lower range reflects estimated blood collection volume without CTC assessment, upper range reflects estimated blood collection volume with CTC assessment.

Table 10: Phase 2a: Approximate Blood Sample Volumes Collected

TEST▼	**Blood Sample Volumes (mL)**								
	SCR	**C1**			**C2**		**C3-4**	**C5+**	
STUDY DAY►	**D–28 to D-1**	**D1**	**D8**	**D15**	**D1**	**D15**	**D1**	**D1**	**30-day FU**
WINDOW (days)►			**± 2**	**± 2**	**± 3**	**± 3**	**± 5**	**± 5**	
PG blood sample	6								
Hematology[a]	8	8	8	8	8	8	8	8	8
Chemistry[a]	8	8	8	8	8	8	8	8	8
Coagulation tests[a]	8	8	8	8	8	8	8	8	8
CRP[a]	5	5	5	5	5		5	5	5
CTCs[b]		20					20[b]	20[b]	20
PSA	10	10			10		10	10	10
HIV and Hepatitis A/B/C tests	9								
Pharmacodynamics blood samples		48.5[c]		5	31		31	31	31
PK blood samples		36		36	18	18	18	6	6
TOTAL VOLUME	**54**	**143.5[c]**	**29**	**70**	**88**	**42**	**88–108[d]**	**76–96[d]**	**96**

30-day FU = 30-day follow-up visit; CRP = c-reactive protein; CTCs = Circulating Tumor Cells; PG = pharmacogenomics; PK = pharmacokinetic; SCR = Screening

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

[b] CTCs assessed every 9 weeks (± 7 days) for the first 24 weeks of treatment (pre-C4, pre-C7, pre-C10), then every 12 weeks after (pre-C14, pre-C18, etc.), or more frequently as clinically indicated if at least 5 cells/7.5 mL blood detected at baseline.

[c] Subjects receiving abiraterone, an extra 10 mL of blood drawn for ARv7 testing on C1D1 (further details are in laboratory manual). Subjects receiving olaparib will have an estimated 38.5 mL of PD pharmacodynamics blood samples (121.5 mL total) drawn on C1D1.

[d] Lower range reflects estimated blood collection volume without CTC assessment, upper range reflects estimated blood collection volume with CTC assessment.

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+ abiraterone acetate + prednisone or PLX2853 + olaparib 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

For all subjects, treatment response will be defined as:

- Objective response by RECIST v1.1 with a minimum interval for confirmation of CR and PR of 4 weeks and/or
- PSA decline of ≥50% from baseline, confirmed by a second consecutive PSA assessment at least 3 weeks later

- Conversion of circulating tumor cell count (CTC) to <5 cells/7.5 mL blood nadir confirmed by an additional assessment at least 3 weeks later (for subjects with a CTC count of ≥5 cells/7.5 mL blood at baseline)

Treatment failure will be defined as:

- Progression by RECIST v1.1 and/or
- Progression by bone scan with a confirmatory scan ≥6 weeks later and/or
- PSA progression per PCWG3 (a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, occurring at least 12 weeks from start of treatment, and confirmed by a second consecutive value obtained at least three weeks later). PSA progression alone does not necessitate treatment discontinuation.

Radiographic progression-free survival (rPFS) is defined by either RECIST v1.1 progression and/or progression on bone scan. It will be calculated for each subject as the number of days from the first day of treatment to the first occurrence of radiographic progression or death from any cause. If no event exists, then rPFS will be censored at the last completed disease assessment on study. The rPFS time will always be derived based on scan/assessment dates not visit dates. When the Investigator is in doubt as to whether PD has occurred and therefore reassesses the subject at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Duration of response (DOR) will be calculated for each subject with a response as the time from date of first documented, confirmed response (CR or PR) using RECIST v1.1 and PCWG3 until date of documented progression or death from any cause.

Best Overall Response (BOR) per RECIST v1.1 will be calculated for each subject with a minimum interval for confirmation of CR and PR of 4 weeks. The minimum interval from baseline to stable disease (SD) is 6 weeks.

Overall survival (OS) will be calculated for each subject as the number of days from the first day of treatment (Cycle 1 Day 1) to the date of death from any cause. If a subject is lost to follow-up, OS is censored at the date of last contact.

Time to PSA progression will be calculated as number of days from first date of treatment (Cycle 1 Day 1) to the date of initial PSA progression per PCWG3 confirmed at least 3 weeks later.

Duration of PSA response will be calculated for each subject with a PSA response as the time from date of first documented, confirmed response (CR or PR) using PCWG3 until date of documented progression confirmed at least 3 weeks later, or death from any cause.

Time to first SSRE defined as one or more of the following:

- Use of radiation therapy to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation is required.
- Occurrence of spinal cord compression. Radiologic documentation required.
- Orthopedic surgical intervention for bone metastasis.

8.7 Safety Analysis

Safety variables to be assessed will include assessment of AEs, physical examinations, laboratory test results (hematology, clinical chemistry, coagulation, serum inflammation markers, and urinalysis), electrocardiogram, MUGA/ECHO, weight, and vital signs.

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.

8.8 Pharmacokinetics, Pharmacodynamics, Biomarkers

8.8.1 Pharmacokinetic Analysis

The PK parameters of PLX2853, abiraterone, and olaparib will be assessed by measuring the AUC from time zero to time of last measurable concentration postdose ($AUC_{0\text{-last}}$), AUC from time zero to 24 hours postdose ($AUC_{0\text{-}24}$), 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, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate.

8.8.2 Pharmacodynamic and Other Biomarker Analysis

Planned biomarker analyses for pharmacodynamics 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 CTC status

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

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

8.9 Analysis and Sample Size

8.9.1 Phase 1b – PLX2853 + Abiraterone Acetate + Prednisone Combination and PLX2853 + Olaparib Combination Analysis and Sample Size

Both the PLX2853 + abiraterone acetate + prednisone combination and the PLX2853 + olaparib combination will be evaluated using a standard "3+3" design in order to determine the MTD/RP2D of PLX2853 for each combination, taking into consideration safety, PK, and PD 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.

8.9.2 Phase 2a (Dose Expansion) – PLX2853 + Abiraterone Acetate + Prednisone Combination Analysis and Sample Size

Efficacy of PLX2853 + abiraterone acetate + prednisone will be investigated in a cohort of subjects with mCRPC. Phase 2a will enroll up to 19 evaluable subjects using a Simon's 2-stage design in which initially 9 evaluable subjects are enrolled. If 2 or more responders are observed in 9 evaluable subjects, another 10 evaluable subjects will be enrolled for a total of 19 subjects. If 6 or more responders are observed, the study has 80% power with alpha of 0.05 to reject the RR of 15% in favor of the RR of 40%. Recruitment will stop if no more than 1 responder is observed after the initial 9 subjects have been accrued. ORR will be summarized along with a 95% confidence interval (CI). A 2-sided 95% CI will be calculated for the true response rate based on the Clopper-Pearson method.

Safety and PK 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.

8.9.3 Phase 2a (Dose Expansion) – PLX2853 + Olaparib Combination Analysis and Sample Size

Efficacy of PLX2853 + olaparib will be investigated in a cohort of subjects with mCRPC. Phase 2a will enroll up to 58 evaluable subjects using a Simon's 2-stage design in which initially 28 evaluable subjects are enrolled. If 16 or more responders are observed in 28 evaluable subjects, another 30 evaluable subjects will be enrolled for a total of 58 subjects. If 38 or more responders are observed, the study has 80% power with alpha of 0.05 to reject the RR of 54% in favor of the RR of 70%. Recruitment will stop if no more than 15 responders are observed after the initial 28 subjects have been accrued. ORR will be summarized along with a 95% confidence interval (CI). A 2-sided 95% CI will be calculated for the true response rate based on the Clopper-Pearson method. Safety, PK, and PD 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.

8.10 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, vital signs, hematology and chemistry laboratory studies, 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, Serious Adverse Events, and Adverse Events of Special Interest

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, and AESIs, as defined in Section 9.3.1, that occur during the course of the study as defined in Section 9.3 must be reported within 24 hours 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 and are also available online at: http://ctep.cancer.gov/reporting/ctc.html. In those cases where the NCI CTC criteria do not apply, intensity should be defined according to the following criteria:

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

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

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

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

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 24 hours of the knowledge of the event. SAEs 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 and do not need to be reported to Plexxikon or its designee within 24 hours 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 24 hours of the knowledge of the event.

9.3.1 Adverse Events of Special Interest

At present, there are no adverse events of special interest for PLX2853.

At present, adverse events of special interest for olaparib include: any event of MDS/AML, new primary malignancy, or pneumonitis should be reported to the Sponsor whether it is considered a non-serious AE (e.g., non-melanoma skin cancer) or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

AESIs will be reported per Section 9.2.

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, abiraterone acetate, prednisone, or olaparib in an amount at least 40% higher than the prescribed dose on any given day. 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 the female partner of a study subject becomes pregnant or suspects she is pregnant while the subject is participating in this study or up to 90 days after completing study treatment, he must inform his treating physician immediately. 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 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, IB, informed consent form, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator or the Sponsor, as allowable by local regulations.

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 in accordance with 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 the 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 lack of efficacy
- 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

- Hemoglobin and hematocrit
- White blood cell (WBC) count with differential (absolute)
- Platelet count

Blood Chemistry

- Sodium
- Potassium
- Chloride
- CO_2
- Calcium
- Phosphorus
- Amylase
- Lipase
- Magnesium
- Glucose
- Blood urea nitrogen
- Creatinine[a]
- Uric acid
- Albumin
- Total protein
- Testosterone
- Total bilirubin
- Direct bilirubin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (AP)
- Lactate dehydrogenase (LDH)
- Gamma-glutamyl transferase (GGT)
- Hemoglobin A1c (Hgb A1c)

[a] Creatinine clearance (CrCL) will be collected at all timepoints creatinine is assessed. CrCL can be measured or calculated per Cockcroft-Gault (Cockcroft 1976) [age in years, weight (wt) in kilograms]:
For serum creatinine concentration in mg/dL:
CrCl = (140 - age) × (wt) / 72× serum creatinine (mg/dL)
For serum creatinine concentration in µmol/L:
CrCl = (140 - age) × (wt) / 0.81 × serum creatinine (µmol/L).

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
- Nitrites
- Ketones/acetone
- Hemoglobin/blood
- Casts or other microscopic findings

Viral Serology Tests

- Hepatitis A virus immunoglobulin M
- Hepatitis B virus surface antigen
- Hepatitis C antibody (if positive, confirmed by HCV ribonucleic acid)
- HIV

Blood Tumor Response Assessment

- Prostate-specific antigen (PSA)
- Circulating Tumor Cells (CTC) per CELLSEARCH System

Plasma Samples for PK

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

Blood Biomarkers and Pharmacodynamics

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

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

Paired Biopsy Tissue Response Biomarkers

- c-Myc and androgen receptors
- 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: STRONG CYP3A4 AND/OR CYP2C8 INHIBITORS AND INDUCERS AND CYP2D6 SUBSTRATES WITH A NARROW THERAPEUTIC INDEX

CYP3A4 and/or CYP2C8 Strong Inhibitors

- Protease inhibitors
  - Ritonavir
  - Indinavir
  - Nelfinavir
- Macrolide antibiotics
  - Erythromycin
  - Telithromycin
  - Clarithromycin
- Azole antifungals
  - Voriconazole
  - Ketoconazole
  - Itraconazole
- Chloramphenicol (antibiotic)
- Nefazodone (antidepressant)
- Bergamottin (constituent of grapefruit juice)
- Aprepitant (antiemetic)
- Verapamil (calcium channel blocker)
- Gemfibrozil (hypolipidemic)
- Thiazolidinedione (antidiabetic)
- Montelukast (Leukotriene receptor antagonist)
- Quercetin (anti-inflammatory)

CYP3A4 and/or CYP2C8 Strong Inducers

- Anticonvulsants, mood stabilizers
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
- Non-nucleoside reverse transcriptase inhibitors
  - Efavirenz
  - Nevirapine
  - Etravirine
- Phenobarbital (barbiturate)
- Rifampicin (bactericidal)
- Modafinil (stimulant)
- Hyperforin (constituent of St John's Wort)
- Cyproterone (antiandrogen, progestin)

CYP2D6 Substrates

- Amiodarone
- Dosulepin
- Flecainide
- Sotalol
- Pimozide
- Procainamide
- Theophylline

This list is not comprehensive and subject to change and all medications should be reviewed prior to administering.

APPENDIX 3: RECIST CRITERIA VERSION 1.1

From: Eisenhauer 2009

Measurability of Tumor at Baseline

Definitions

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

Measurable tumor lesions

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

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

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

Non-measurable tumor lesions

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

Special considerations regarding lesion measurability

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

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same 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 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 five 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 (FDGPET)

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' (Table 15).

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 11 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 12 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 11: 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 12: 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 13: 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 11, Table 12, and Table 13.

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 mkt)
- Quinidine
- Sotalol
- Ritonavir
- Indinavir
- Nelfinavir

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

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

Anti-cancers
- Arsenic trioxide
- Vandetanib

Anti-depressants, SSRIs
- Citalopram
- Escitalopram

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

Anti-malarials
- Chloroquine
- Halofantrine

Antilipemic
- Probucol (Removed from US Market)
- Ondansetron

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

Anesthetics, general
- Propofol
- Sevoflurane

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

This list is not comprehensive and subject to change 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: PCWG3 CASTRATION-RESISTANT PROSTATE CANCER CLINICAL TRIAL RECOMMENDATIONS AND CRITERIA

Table 2. Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations

Assessment	PCWG2 (2008)	PCWG3 (2015)
Histology	Not addressed	Adenocarcinoma
		Adenocarcinoma with small-cell or neuroendocrine features
		Small-cell carcinoma
		Report Gleason sum for primary
		Consider rebiopsy of metastatic disease
Clinical	History and physical examination	Age, pain, analgesic consumption, performance status, comorbidity assessment, history, and physical examination; prior local therapy; TNM stage at diagnosis; and PSA
Prior systemic treatment	Pre- and postchemotherapy	Record each line of systemic therapy (single agent or combination) in order of administration, including start and stop dates, dose(s), and schedule(s), the disease state in which it was administered, and response (resistant *v* sensitive) on the basis of PSA if appropriate
		Record type of progression on prior therapy (PSA, radiographic [bone, nodal, visceral], clinical [eg, pain escalation])
Prior radiation therapy	Not addressed	Site, administered dose per fraction and treatment duration
Blood-based biomarkers	PSA	Host: CBC with differential, ALK, kidney/liver function, albumin, LDH, testosterone*
	Testosterone	Tumor: PSA and cPSA kinetics
		Optional: CEA, chromogranin A, neuron-specific enolase, CTC enumeration
Imaging		
Prostate/prostate bed	Endorectal MRI	Retained, cross-sectional imaging of prostate region if applicable
Nodal	CT: Only nodes ≥ 2 cm were assessed for change in size	CT or MRI:
		Nodes ≥ 1.5 cm in the short axis are considered measurable; nodes ≥ 1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes less than 1.0 cm in the short axis are nonpathologic
		Record pelvic and extrapelvic (retroperitoneal, mediastinal, thoracic, other) nodal disease separately; up to five nodes in total
		Record new lesions *v* growth of pre-existing lesions, and sites of new lesions
Visceral	CT: reported as visceral per RECIST	CT or MRI:
		Record individual sites of spread (lung, liver, adrenal, CNS) separately; up to five lesions per site
		Lesions ≥ 1.0 cm in the longest dimension are considered measurable
		Record new lesions *v* growth of pre-existing lesions, and sites of new lesions
Bone	^{99m}Tc MDP	Record new lesions and sites of new lesions

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Table 2. Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations (continued)

Assessment	PCWG2 (2008)	PCWG3 (2015)
Tumor profiling for determinants of prognostic, predictive, and resistance biomarkers	Not addressed	Consider rebiopsy of metastatic or locally recurrent lesion(s) for biologic characterization
Patient-reported outcomes	None	Pain assessment, opiate analgesia consumption, physical functioning (functional status), health-related quality of life; consider fatigue and PRO-CTCAE. Validated PRO instruments strongly recommended

Abbreviations: ALK, alkaline phosphatase; CBC, complete blood count; CEA, carcinoembryonic antigen; CT, computed tomography; CTCs, circulating tumor cells; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; 99mTc MDP, 99mTc methylene diphosphonate.

*Ultrasensitive testosterone measures may be indicated where appropriate on the basis of drug under study and context.

Source: Scher 2016

Table 3. Criteria for Progression at Trial Entry by Disease Manifestation

Variable	PCWG2 (2008)	PCWG3 (2015)
Blood-based		
PSA	Obtain sequence of rising values at a minimum of 1-week intervals	Retained
	2.0 ng/mL minimal starting value	1.0 ng/mL is the minimal starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma
	Estimate pretherapy PSADT if at least three values available ≥ 4 weeks apart	Retained
Imaging		
Nodes	Nodal progression sufficient for trial entry independent of PSA	Retained
	Measurable lesions not required for entry	Retained
	Use RECIST to record nodal lesions as target or nontarget	Modified RECIST 1.1 criteria, separate pelvic and extrapelvic disease, up to five nodal lesions total recorded
	Only lymph nodes ≥ 2 cm in diameter (long axis) were actionable as progressive disease	Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed
		If the node progresses to ≥ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable
		For existing pathologic adenopathy, progression is defined per RECIST 1.1
	Record presence of nodal and/or visceral disease separately	Retained with modification
		Nodal sites: Locoregional: pelvic only Extrapelvic: retroperitoneal, mediastinal, thoracic, or other
Viscera	Visceral progression sufficient for trial entry independent of PSA	Retained but recorded separately by site of spread (lung, liver, adrenal, CNS); up to five lesions per site of spread
	Measurable lesions not required for entry	Retained
	Use RECIST to record visceral lesions as target or nontarget	Retained
	Record presence of nodal and/or visceral disease separately	Retained with modification
		Visceral sites: lung, liver, adrenal, CNS

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Table 3. Criteria for Progression at Trial Entry by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
Prostate/prostate bed (primary site)	Record prior treatment of primary tumor	Retained
	Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease	Retained
Bone	Two new lesions	Retained
	Confirm ambiguous results by other imaging modalities (eg, CT or MRI)	Retained, but only positivity on the bone scan defines metastatic disease to bone
Other sites of disease	Patients with treated epidural lesions and no other epidural progression are eligible	Retained
Type of progression at trial entry	Not addressed	Report separately: PSA only Bone only ± nodal disease Nodal disease only (no bone disease present) Visceral (lung, liver, adrenal, CNS) disease (± other sites) Record new lesions and site of new lesions v growth of pre- existing lesions, or both
Other markers		
Patient-reported outcomes	Not addressed	For pain palliation analyses, presence of clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) is a prerequisite; for pain progression analyses, patients may have any level of pain at baseline, including no pain

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PET, positron emission tomography; PSA, prostate-specific antigen; PSADT, PSA doubling time; RECIST, Response Evaluation Criteria in Solid Tumors.

Source: Scher 2016

Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation

Variable	PCWG2 (2008)	PCWG3 (2015)
Histology	Not addressed	Encourage rebiopsy of metastatic sites or local recurrence at progression to evaluate for histologic (ie, neuroendocrine/small cell) transformation; in the context of clinical trials, encourage rebiopsy for biomarker assessment
Blood-based markers		
PSA	Recognize that a favorable effect on PSA may be delayed for ≥ 12 weeks, even for a cytotoxic drug	Retained
	Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression	Retained
	Ignore early rises (before 12 weeks) in determining PSA response	Retained
	For control/relieve/eliminate end points:	For control/relieve/eliminate end points:
	Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot	Retained, except with timing (8-9 or 12 weeks) depending on trial design
		Separately report the proportion of patients who have undergone radical prostatectomy and achieved a nadir less than 0.2 ng/mL *v* primary radiation therapy–treated patients who achieved a nadir less than 0.5 ng/mL
		Describe absolute changes in PSA over time from baseline to best response
	For delay/prevent end points (progression):	For delay/prevent end points (progression):
	After decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25%	Retained (standards for reporting PSA progression date may not indicate a need to stop treatment)
	Recording the duration of PSA decline of little value	Retained
	No decline from baseline: PSA progression ≥ 25% increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks	Relate to mechanism of drug and anticipated timing of potential favorable/unfavorable effects on PSA, if present

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Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
CTC	Not addressed	Enumerate at the start of treatment: Record as favorable (four or fewer cells per 7.5 mL of blood) or unfavorable (five or more cells per 7.5 mL)
		If unfavorable, monitor for changes after treatment
		For control/relieve/eliminate end points:
		Report as change from unfavorable (five or more cells per 7.5 mL of blood) to favorable (four or fewer cells per 7.5 mL) and separately, the percent change from baseline using a waterfall plot
		For delay/prevent end points: no validated definition exists (however, rising CTC counts are associated with a poor prognosis)
LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, urine *N*-telopeptide, hemoglobin, NLR	Not addressed	Descriptively report changes over time, may include the proportion showing normalization of a given biomarker and/or waterfall plots of percent change from baseline in a given biomarker
		Report institutional normal ranges to determine normalization of a given biomarker
Imaging biomarkers: nodal and visceral		
For control/relieve/eliminate end points		
General	Record changes in nodal sites separately from visceral sites	Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately
	Use RECIST with caveats:	Record up to five lesions per site of disease
		Use RECIST 1.1 with caveats:
	Record changes in size using waterfall plot	Record changes in size using waterfall plot
	Confirm favorable change with second scan	Confirm favorable change with second scan
	Record complete elimination of disease at any site separately	Record complete elimination of disease at any site separately
Nodes	Only report changes in lymph nodes that were ≥ 2 cm in the long axis at baseline	Only report changes in lymph nodes that were ≥ 1.5 cm in the short axis
		Record changes in pelvic (regional) nodes *v* extrapelvic (distant/metastatic) nodes separately
Visceral	Use RECIST with caveats above	Use RECIST 1.1 with caveats: Record changes in liver, lung, adrenal, and CNS separately Only report changes in lesions ≥ 1.0 cm in the longest dimension

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Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
For delay/prevent end points		
Nodal and visceral	Use RECIST criteria for progression, with additional requirement that progression be confirmed by a second scan ≥ 6 weeks later (the second scan is particularly important when anticipated effect on PSA is delayed, or for biologic therapies)	General: Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately Use RECIST 1.1 but clearly record type of progression (growth of existing lesions *v* development of new lesions) separately by site The recommendations apply to both nmCRPC and mCRPC Record up to five lesions per site of spread Report the proportion who have not progressed at fixed time points (6 or 12 months)
	Note that for some treatments, a lesion may increase in size before it decreases	Retained
Nodal	As above	Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

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Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
Imaging biomarkers: bone		
Metastatic	For control/relieve/eliminate end points:	For control/relieve/eliminate end points:
	Record changes as improved or stable (no new lesions) or worse (new lesions)	Retained with addition of resolved bone lesion
	Changes in intensity of uptake alone do not constitute progression or regression	Retained
	No new lesions: continue therapy in absence of other signs of progression	Retained
	New lesions (See Progression below)	Retained
	For delay/prevent end points (progression):	For delay/prevent end points (progression):
	Progression:	Progression:
	Exclude pseudoprogression in the absence of symptoms or other signs of progression	Retained
	At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (212 rule)	
	If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented	Retained
	For all scans after the first post-treatment scan, at least two new lesions	For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
	Date of progression is the date of the scan that first documents the second lesion	Retained
	Changes in intensity of uptake alone do not constitute either progression or regression	Retained
		Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
nmCRPC	Not addressed	Nonmetastatic to metastatic progression:
		Any new unequivocal bone lesion, except if that lesion appears in the first post-treatment scan; in that case, document the event, continue treatment until 2 additional new lesions appear, and record both events

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Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
Patient-reported outcomes	Consider independently of other outcome measures	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use)
	For control/relieve/eliminate end points:	For control/relieve/eliminate end points:
	Document pain and analgesia at entry with a lead-in period repeatedly at 3- to 4-week intervals	Serial (eg, daily × 7 days) assessments at each time point can and measure improve the stability of values
	Perform serial assessments of global changes in HRQoL, urinary or bowel compromise, pain management, additional anticancer therapy	Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement
	Ignore early changes (≤ 12 weeks) in pain or HRQoL in absence of compelling evidence of disease progression	
	For delay/prevent end points:	For delay/prevent end points:
	Confirm response or progression of pain or HRQoL end points ≥ 3 weeks later	Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use)
		Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later)
		Time to deterioration of physical function and/or HRQoL scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire

Abbreviations: CTC, circulating tumor cell; HRQoL, health-related quality of life; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; NLR, neutrophil/ lymphocyte ratio; nmCRPC, nonmetastatic castration-resistant prostate cancer; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PSA, prostate- specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

Source: Scher 2016