Abbreviated Title: PLX038 and Rucaparib
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Title: Phase I/II trial of PLX038 (PEGylated SN38) and Rucaparib in Solid tumors and Small Cell Cancers

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Drug Name:	PLX038 (PEGylated SN38)	Rucaparib
IND Number:	145310	145310
Sponsor:	CCR, NCI	CCR, NCI
Manufacturer:	ProLynx LLC	Clovis Oncology, Inc.
Supplier:	ProLynx LLC	Clovis Oncology, Inc.

Safety Monitoring Committee (SMC): NCI SMC

PRÉCIS

Background:

- We hypothesize that a dose-escalation strategy that incorporates tumor targeted DNA-damaging chemotherapy and DNA-damage response (DDR) inhibitors could allow safe and effective administration of DDR inhibitor-chemotherapy combination.
- PLX038 is a PEGylated conjugate of SN38 with improved properties including increased solubility, higher exposure and longer half-life. SN-38 is the active metabolite of CPT-11 (irinotecan) that inhibits topoisomerase 1 (Top1) and causes DNA strand breakage. As a specific DNA damaging agent, SN-38 enhances cell kill in tumors deficient in the DNA-damage response and when combined with inhibitors of the DDR.
- Rucaparib is a potent oral poly ADP ribose polymerase (PARP) inhibitor that is approved for the maintenance treatment of participants with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- We hypothesize that the combination of PLX038 plus rucaparib is more efficacious than either agent alone.

Objectives:

- Phase I: To identify the maximum tolerated dose (MTD) of PLX038 in combination with rucaparib.
- Phase II: To assess the efficacy with respect to clinical benefit rate (CBR) (CR+PR+SD) for 4 months according to Response Evaluation Criteria (RECIST 1.1) of a combination of PLX038 and rucaparib in participants with small cell lung cancer and extra-pulmonary small cell carcinomas.

Eligibility:

- Subjects with histologically confirmed solid tumors (Phase I) OR histologically or cytologically confirmed small cell lung cancer (SCLC) (Phase II) OR histologically or cytologically confirmed extra-pulmonary small cell carcinomas (Phase II).
- Age ≥18 years
- Subjects must have evaluable or measurable disease.
- ECOG performance status ≤ 2
- Adequate organ function

Design:

- This is an open label Phase I/II trial accruing initially one cohort to determine maximum tolerated dose (MTD) of combined treatment of PLX038 and rucaparib (Phase I); and to examine the safety and efficacy of PLX038 in combination with rucaparib in the following cohort (Phase II).
- PLX038 will be administered by IV infusion on day 1 of every 21-days cycle, rucaparib will be administered PO twice daily on days 6 to 19 of every cycle.

- Treatment will continue until progression or unacceptable toxicity.
- Biomarkers of participant response to treatment will be investigated in an exploratory manner pre and post-treatment.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 Study Objectives

1.1.1 Primary Objectives

- Phase I: To identify the maximum tolerated dose (MTD) of PLX038 in combination with rucaparib.
- Phase II: To assess the efficacy with respect to clinical benefit rate (CBR) (CR+PR+SD) for 4 months according to Response Evaluation Criteria (RECIST 1.1) of a combination of PLX038 and rucaparib in participants with small cell lung cancer.

1.1.2 Secondary Objectives

- To assess safety and tolerability of combined treatment of PLX038 and rucaparib
- To determine the progression-free survival (PFS) in Phase II
- To determine overall survival (OS) in Phase II
- To assess the clinical response rate (CRR) (CR+PR) according to Response Evaluation Criteria (RECIST 1.1) in participants with small cell lung cancer.

1.1.3 Exploratory Objectives

- To identify pharmacodynamic markers of response including γ H2AX
- To identify predictors of response
- To assess pharmacokinetics of PLX038 and rucaparib
- To preliminarily assess the clinical outcomes of participants with extrapulmonary SCLC
- To describe and investigate the interference of PLX038 with coagulation assays

1.2 Background and Rationale

PARP inhibitors are now approved for various indications and are under investigation for various tumor types. Despite promising preclinical data, chemotherapy-PARP inhibitor combinations have proved challenging in clinic. Dose limiting toxicities, specifically myelosuppression, has severely limited the ability to dose escalate both PARP inhibitors (PARPi) and chemotherapy in several clinical studies [1-7] (**Table 1**). We hypothesize that a dose-escalation strategy that incorporates tumor targeted DNA-damaging chemotherapy and DDR inhibitors could allow higher dose administration of DDR inhibitor-chemotherapy combinations. Combinations of PARP inhibitors with DNA damaging chemotherapy is likely to be most effective in high replicative (HR) stress tumors[8] and in tumors with defects in DNA repair pathways including HR stress tumors such as ovarian, breast, and prostate cancers.

Table 1. Trials of PARP inhibitors with topoisomerase inhibitors

Combination		MTD	Topo 1 inhibitors % of MTD	PARPi % of MTD	DLT	Ref
Irinotecan	Olaparib	Irinotecan 200 mg/m^2; q3w Olaparib 50 mg qd days 1-21	57%	6%	Diarrhea, myelosuppression	[5]
		Irinotecan 125 mg/m^2 q2w Olaparib 50 mg bid days 1-5	≈69%	≈12%	Anorexia/fatigue	
Irinotecan	Veliparib	Irinotecan 100 mg/m^2 days 1, 8; subsequent q3w Veliparib 40 bid days 1-14	≈80	≈10%	Diarrhea, fatigue, myelosuppression	[2]
Topotecan	Olaparib	Topotecan 1 mg/m^2 on days 1-3; subsequent q3w Olaparib 100 mg bid days 1-21	≈40%	25%	Myelosuppression	[3]
Topotecan	Veliparib	Topotecan 0.6 mg/m^2 on days 1-5; subsequent q3w Veliparib 10 bid days 1-5	40%	≈3%	Myelosuppression	[4]

1.2.1 Small cell lung cancer (SCLC) and extrapulmonary small cell carcinoma.

Small cell lung cancer (SCLC) is the most aggressive and lethal form of lung cancer. Because of frequent chromosomal alterations, dysregulation of genes that promote replication origin firing (*e.g.*, MYC) and the high expression of DNA damage repair proteins, we have postulated that SCLC has high levels of endogenous replicative DNA replication forks due to various perturbations that interfere with replication [9].

SCLC represents 15% of all lung cancers, with an annual incidence of over 34,000 cases in the United States alone. SCLC is characterized by rapid doubling time, high growth fraction and early and widespread metastatic involvement [10]. Response rates to first-line chemotherapy are exceptionally high, on the order of 60% to 70%. Unfortunately, these responses are also disappointingly transient, with median PFS of <5 months [11, 12] and nearly all participants relapse within one year. Extensive-stage SCLC is generally unresponsive to chemotherapy at relapse, and fewer than 5% of participants survive for two years [10]. Treatment of SCLC as well as survival after a diagnosis of SCLC have not changed substantially in the past 30 years [13].

Due to an urgent need for effective interventions in this disease, SCLC was singled out by the NCI as a designated "recalcitrant" cancer based on incidence rate, exceptionally high lethality, and the lack of substantial therapeutic progress made over several decades [14].

At the time of diagnosis most participants (60-70%) have extensive-stage (ES) disease, defined as cancer that has spread beyond the ipsilateral lung and regional lymph nodes and cannot be included in a single radiation field [10]. The primary treatment modality for participants with ES-SCLC is systemic chemotherapy consisting of platinum and etoposide followed by prophylactic cranial irradiation in participants with a response [15]. Both topotecan and irinotecan are active in relapsed SCLC. Topotecan is Food and Drug Administration (FDA)-approved for participants with SCLC with chemotherapy-sensitive disease after failure of first-line chemotherapy.

Extrapulmonary small cell carcinoma is a distinct clinicopathologic entity that can arise in a wide range of extrapulmonary sites. These tumors have been described most frequently in the bladder, prostate, esophagus, stomach, colon and rectum, gallbladder, larynx, salivary glands, cervix, and skin. They are extremely rare and management of systemic disease with chemotherapy is patterned the approach used in SCLC[16].

Camptothecins are an active drug class in SCLC. Both irinotecan [17] and topotecan [18] are used in the first and second line setting respectively as part of standard care.

Drugs that target DNA damage response (DDR), including PARP inhibitors, have shown promising activity against SCLC in pre-clinical models and in early clinical trials. Proteomic profiling of a large panel of SCLC cell lines led to the observation that PARP1, Chk1, and several other DNA repair proteins are expressed at high levels in SCLC [19]. These studies also confirmed PARP1 overexpression in participant tumors at the protein level by immunohistochemistry and at the mRNA level. Based on this finding, several PARP inhibitors were tested in pre-clinical models of SCLC. Olaparib, rucaparib, and talazoparib (BMN-673) all demonstrated striking single agent activity in a majority of SCLC cell lines tested. Furthermore, the addition of a PARP inhibitor to standard chemotherapies (e.g., cisplatin, etoposide and/or topotecan) and radiation further potentiated their effect [20]. In animal models including xenografts and participant-derived xenografts (PDXs), talazoparib has demonstrated significant anti-tumor activity as a single agent, comparable or superior to cisplatin [21].

Following these observations, several clinical trials were initiated to investigate the effects of PARP inhibition in SCLC participants. Single-agent talazoparib was tested in an expansion cohort of participants with platinum-sensitive SCLC relapse [22]. Two of 23 participants had a partial response (PR; objective response rate (ORR), 9%, with duration of response 12.0 and 15.3 weeks, respectively), and a further 4 had SD lasting at least 16 weeks (CBR, 26% ≥16 weeks). Additional studies have also evaluated the combination of PARP inhibitors and DNA damaging chemotherapy in SCLC. Based on phase 2 data showing activity of temozolomide (TMZ) in relapsed SCLC and

preclinical data demonstrating activity of TMZ in combination with PARP inhibitors [23], clinical trials have tested this combination in SCLC. In one study [24], 104 relapsed SCLC participants were randomly assigned 1:1 to oral veliparib or placebo plus temozolomide. Four-month PFS and median OS did not differ between the two arms, whereas a significant improvement in ORR was observed with TMZ/veliparib. SLFN11 expression was associated with improved PFS and OS in participants receiving TMZ/veliparib.

In preclinical SCLC models, PARP inhibition has been reported to down regulate key components of the DNA repair machinery and enhance the efficacy of chemotherapy [19]. PARP inhibition sensitizes cancer cells both to cytotoxic chemotherapy, such as alkylators (temozolomide, cyclophosphamide) or camptothecins (irinotecan, topotecan) and to ionizing radiation - all of which induce DNA damage requiring base excision repair (BER) [25]. PARP inhibitors are highly effective in combination with camptothecins in tumors with and without defects in homologous recombination [26-29]. The Pommier laboratory has demonstrated highly synergistic activity of olaparib in combination with camptothecins [29]. They observed that the synergistic activity is due to its catalytic PARP inhibitory activity rather than due to trapping of PARP-DNA complexes.

1.2.2 SN-38 and PLX038

SN-38 is the active metabolite of CPT-11 (irinotecan) that inhibits topoisomerase I and causes DNA strand breakage. As a specific DNA damaging agent, SN-38 enhances cell kill in tumors deficient in the DNA-damage response (DDR; e.g. BRCA1/2-deletions) and when combined with inhibitors of the DDR (e.g. PARP inhibitors). PLX038 (PEG_{40kDa}~SN-38) is a 4-arms 40 kDa PEG that has SN-38 attached by a slowly cleavable releasable linker to the ends of each arm; the species-independent in vivo release rate of SN-38 is very long - 350 hr. [30].

For complete safety and efficacy information, refer to investigator brochure.

1.2.2.1 Preclinical efficacy studies of PLX038 and PLX038A

Although the renal clearance of PLX038 in the mouse was too rapid to allow its use in this animal model, preclinical pharmacology studies showed high antitumor activity – comparable or better than CPT-11 – in numerous xenografts in the nude rat.

An analog of PLX038 – PLX038A – was designed to mimic human pharmacokinetics of PLX038 in the mouse, and preclinical studies were performed using the BRCA1-deficient, TNBC MX-1 xenograft the mouse. Single, nontoxic doses of PLX038A completely inhibited growth of MX-1 tumors and shrank massive tumors to undetectable levels. Using PET-imaging studies of an ^{89}Zr surrogate of PLX038, we showed that PEG_{40kDa}~SN-38 accumulated to a very high ~15% ID in the tumor and remained there for long periods ($t_{1/2}$~14 days). Hence, we envisioned that we could "pre-load" a tumor with PEG_{40kDa}~SN-38, allow the drug to clear systemically, and then treat with a PARP inhibitor; here, only the tumor would be exposed to both drugs concomitantly, and marrow toxicity of the combination might not occur. When used in combination with sub-therapeutic QD dose PARP inhibitor, talazoparib, a single low sub-therapeutic dose of PLX038A (10% of single dose) caused complete tumor inhibition and shrinkage of large tumors. Importantly, when the same sub-therapeutic dose of PLX038A was administered as a single agent, followed by a systemic washout of drug (4-half-lives of renal elimination), administration of the same sub-therapeutic QD dose of PARP inhibitor caused complete growth inhibition. In these combination studies, we did not observe weight loss or marrow toxicity.

1.2.2.2 Preclinical Toxicology of PLX038

Maximum tolerated dose (MTD)/dose range finding (DRF), acute dose, 14 day and 28 day repeat intravenous (IV) PLX038 dosing studies were conducted in rats and monkeys. Based on the dosing studies, the primary target organs are the bone marrow, gastrointestinal tract and skin. The monkey was the more sensitive species.

In rats, single IV doses up to 1,000 mg/kg and repeat weekly injections up to 800 mg/kg was well-tolerated. Rats that received repeat weekly injections of 800 mg/kg had decreased thymic weight and bone marrow hypocellularity attributed to PLX038. High doses of PLX038 caused decreases in clinical chemistries and hematology, increased aPTT and PT and decreased food consumption.

In monkeys, a single large IV dose of 1,000 mg/kg and repeat weekly injections of ≥ 600 mg caused lethality. Cause of death was uncertain. Bone marrow depletion with correlating changes, with or without evidence of secondary infections, were possible contributing factors to the deaths. Macroscopic multifocal red discoloration and acute inflammation of gastrointestinal organs were also noted, probably related to PLX038.

In surviving monkeys, a dose-dependent increase in diarrhea was noted. All animals experienced decreases in clinical chemistries and hematology that were reversible. At autopsy, bone marrow hypocellularity, decreased thymic and spleen size were detected. Macroscopic changes in the gastrointestinal epithelium (inflammation, multifocal lesions) were also noted, thought to be caused by PLX038.

In the 4-week repeat dose study in monkey, small to large cornea pigmentation was observed in monkeys in all treatment groups at the end of the dosing period. In some cornea pigmentation persisted and was still present at the end of the recovery period. Two monkeys in the low dose (200 mg/kg) group that did not have cornea staining on Day 25 developed medium pigmentation on Day 50 suggesting a possible delayed effect. Due to the observation of cornea pigmentation in all treatment groups, no no-effect-level (NOAEL) could be determined in the 4-week repeat dose study.

In both rats and monkeys, histopathology revealed mild to moderate vacuolation in several tissues.

1.2.2.3 Phase 1 dose escalation of PLX038

The Phase 1 dose escalation trials are being performed in single-dose cohorts at MD Anderson, with Dr. Jaffer Ajani as PI, and Theradex Oncology as CRO. **Table 4** shows the current study enrollment through Participant 38 (including 4 screen failure patients) and describes the dose level, cancer type, and other relevant information. To date in the Phase I study D15-11073, 34 patients have received PLX038 treatment at doses ranging from 115 mg/m^2 to 3060 mg/m^2 (corresponding to ~1 to 32 mg/m^2 released SN38) q3w in 21-day cycles. The study is ongoing.

Treatment emergent adverse events (TEAEs) during Study D15-11073 have been reported for all 34 safety evaluable patients as of January 2022. The most common TEAEs have been reported for the system organ classes of gastrointestinal disorders (28 patients, 82.3%), metabolism and nutrition disorders (25 patients, 89.3%) and General System Disorders/Fatigue 11 patients (32.4%). PLX038-related TEAEs during Study D15-11073 have been reported for 25 patients (73.5%) from the safety evaluable population to date. Of the 25 patients with PLX038-related TEAEs, 11 patients (32.4%) had related TEAEs that were ≥Grade 3 in severity. The most common PLX038-related TEAEs were diarrhea (16 patients), nausea (14 patients), decreased appetite (13

patients), vomiting (11 patients), fatigue (10 patients), abdominal pain (5 patients), dehydration (4 patients), hypokalemia (4 patients), neutrophil count decreased (4 patients), and colitis (3 patients).

Of the 34 patients in the safety evaluable population, 16 patients (41.1%) have reported serious adverse events (SAEs) during the study. The most common SAEs reported in the study are diarrhea (6 patients, 17.6%), abdominal pain (3 patients, 8.8%), and dehydration (3 patients, 8.8%).

To date, there are 8 patients (23.5%) who have experienced serious adverse reactions (SARs) that were at least possibly related to study treatment.. Additionally, Patient 001-029 (enrolled in the 2600 mg/m^2 dose level), experienced Grade 3 diarrhea, which was considered a dose limiting toxicity (DLT), during Cycle 1, Day 13 that was definitely related to study therapy and resolved within 4 days of onset. Lastly, Patient 001-031 (enrolled in the 2300 mg/m^2 dose level) experienced possibly related Grade 2 dehydration and definitely related Grade 3 diarrhea on Cycle 1, Day 9. On Cycle 1, Day 13 the patient experienced possibly related Grade 4 dehydration and unrelated Grade 5 embolism, which had a fatal outcome.

Table 2. Serious Adverse Events (N=34 Patients dosed, 16 patients affected *)

Patient	Dose (mg/m2)	Preferred Term (PT)	DLT Toxicity	Grade	Serious	Drug Relationship	Action Taken	Outcome of Event
001-002	172	GI hemorrhage	No	2 - Moderate	Hospitalization	Unrelated	None	Recovered/Resolved
001-005	580	Apnea	No	5 - Fatal	Results in Death	Unrelated	None	Fatal
001-005	580	Cardiac arrest	No	5 - Fatal	Results in Death	Unrelated	None	Fatal
001-005	580	Sepsis	No	4 - Life threatening	Hospitalization	Unlikely	None	Recovered/Resolved
001-005	580	Upper GI hemorrhage	No	5 - Fatal	Results in Death	Unrelated	None	Fatal
001-006	387	Biliary tract infection	No	4 - Life threatening	Hospitalization	Unrelated	None	Recovered/Resolved
001-007	580	Mental status changes	No	1 - Mild	Hospitalization	Unrelated	None	Recovered/Resolved
001-007	580	Peritonitis bacterial	No	3 - Severe	Hospitalization	Unrelated	None	Recovered/Resolved
001-014	3060	Gastric hemorrhage	No	3 - Severe	Hospitalization	Unrelated	None	Recovered/Resolved
001-015	3060	Malignant neoplasm progression	No	5 - Fatal	Results in Death	Unrelated	None	Fatal
001-017	3060	Abdominal pain	No	3 - Severe	Hospitalization	Possible	Dose Discontinued	Recovered/Resolved
001-017	3060	Colitis	No	3 - Severe	Hospitalization	Probable	None	Recovered/Resolved

Patient	Dose (mg/m2)	Preferred Term (PT)	DLT Toxicity	Grade	Serious	Drug Relationship	Action Taken	Outcome of Event
001-017	3060	Hypoalbuminemia	No	4 - Life threatening	Hospitalization	Unrelated	Dose Discontinued	Not Recovered/ Not Resolved
001-017	3060	Hypokalemia	No	3 - Severe	Hospitalization	Possible	Dose Discontinued	Recovered/Resolved
001-018	3060	Dehydration	No	3 - Severe	Hospitalization	Definite	None	Recovered/Resolved
001-018	3060	Diarrhea	No	3 - Severe	Hospitalization	Definite	None	Recovered/Resolved
001-018	3060	Sepsis	No	4 - Life threatening	Hospitalization	Unrelated	None	Recovered/Resolved
001-018	3060	Small intestinal obstruction	No	3 - Severe	Hospitalization	Possible	Dose Discontinued	Recovered/Resolved
001-019	3060	Abdominal pain	No	3 - Severe	Hospitalization	Probable	None	Recovered/Resolved
001-019	3060	Dehydration	No	3 - Severe	Hospitalization	Definite	None	Recovered/Resolved
001-019	3060	Diarrhea	No	3 - Severe	Hospitalization	Definite	None	Recovered/Resolved
001-019	3060	Hypotension	No	3 - Severe	Hospitalization	Definite	None	Recovered/Resolved
001-019	3060	Small intestinal obstruction	No	3 - Severe	Hospitalization	Probable	None	Recovered/Resolved
001-021	2800	Colitis	No	2 - Moderate	Hospitalization	Definite	None	Recovered/Resolved
001-021	2800	Diarrhea	No	2 - Moderate	Hospitalization	Definite	None	Recovered/Resolved
001-021	2800	Hypokalemia	No	3 – Severe	Hospitalization	Definite	None	Recovered/Resolved
001-024	2600	Abdominal pain	No	3 - Severe	Hospitalization	Unrelated	None	Recovered/Resolved
001-024	2600	Enterocolitis	No	2 - Moderate	Hospitalization	Possible	Dose Discontinued	Recovered/Resolved
001-026	2600	Lung infection	No	3 - Severe	Hospitalization	Unrelated	None	Recovered/Resolved

Patient	Dose (mg/m2)	Preferred Term (PT)	DLT Toxicity	Grade	Serious	Drug Relationship	Action Taken	Outcome of Event
001-029	2600	Diarrhea	Yes	3 - Severe	Hospitalization	Definite	Dose Discontinued	Recovered/Resolved
001-031	2300	Diarrhea	Yes	3 - Severe	Hospitalization	Definite	Dose Discontinued	Not Recovered/ Not Resolved
001-031	2300	Embolism	Yes	5 - Fatal	Results in Death	Unrelated	None	Fatal

* Patients may have experience more than one SAE

Three deaths have been reported to date, all of which were considered to be unrelated to study treatment. Patient 001-005 (enrolled in the 580 mg/m2 cohort) developed a fatal upper GI hemorrhage leading to cardiac arrest and apnea. Patient 001-015 (enrolled in the 3060 mg/m2 cohort) died of malignant neoplasm progression. Patient 001-031 (enrolled in the 2300 mg/m^2 dose level), experienced Grade 3 diarrhea (definitely related) and Grade 5 embolism (unrelated), which had a fatal outcome

To date,5 patients (14.7%) have been removed from the study (dose discontinued) due to a serious adverse event (SAEs):

Table 3. Patients Discontinued Due to SAE

Patient	Dose mg/m2	Adverse Event	DLT	Grade	Serious	Drug Relationship	Therapy Given	Action Taken
001-017	3060	Hypokalemia	No	3	Hospitalization	Possible	Yes	Dose Discontinued
	3060	Abdominal Pain	No	3	Hospitalization	Possible	Yes	Dose Discontinued
	3060	Hypoalbuminemia	No	4	Hospitalization	Possible	Yes	Dose Discontinued
001-018	3060	Small Intestinal Obstruction	No	3	Hospitalization	Possible	No	Dose Discontinued
001-024	2600	Enterocolitis	No	2	Hospitalization	Possible	Yes	Dose Discontinued
001-029	2600	Diarrhea	Yes	3	Hospitalization	Definite	Yes	Dose Discontinued
001-031	2300	Diarrhea	Yes	3	Hospitalization	Definite	Yes	Dose Discontinued

Of the 34 dosed patients in the safety evaluable population, 18 patients (52.9%) have reported SAEs during the study. The most common SAEs reported in the study are diarrhea (6 patients, 18.2%), abdominal pain (3 patients, 9.1%), and dehydration (3 patients, 9.1%).

A total of 22 (64.7%) of 34 patients enrolled and dosed in the phase I trial experienced diarrhea. Diarrhea was less frequent at the lower doses; 4/10 (40%) patients who received lower doses (1300 mg/m^2 or lower) had diarrhea compared with 18/24 (75%) patients treated at higher doses (1730-3060 mg/m2). Severe diarrhea was more frequent at the higher doses; all instances of diarrhea were mild at the lower doses, while 13 patients had moderate-severe diarrhea at the higher doses.

Five patients developed neutropenia, including two patients with grade 4 events. All patients with neutropenia were treated at 2600 or 3060 mg/m^2.

As of this report, the PLX038 dose of 3060 mg/m^2 as a single agent has been identified as the maximal administered dose in the D15-11073 study, with associated dose limiting toxicities (DLTs) of Grade 4 neutropenia, and Grade 3 nausea, diarrhea, and small intestinal obstruction. Additionally, the intermediate doses of 2800 mg/m^2 and 2600 mg/m^2 were not tolerated as they caused Grade 3 diarrhea in the two patients treated at each dose level. In all, duration of diarrhea of Grades 1 to 3 experienced by 22 patients ranged from 1 to 35 days, lasting an average of 11 days. The D15-11073 study continues in order to determine the recommended Phase II dose for single agent PLX038 administered on a q3w schedule.

In addition, because of the low liver exposure of SN-38 from PLX038, the metabolite SN-38G formed from UGT1A1 is low, with plasma SN-38-G/SN-38 = 0.3 ± 0.1. Hence, UGT1A1 activity is not expected to play a major role in disposition of PLX038; in recognition of the latter, the FDA has allowed full-dose PLX038 treatment of participants heterozygous in UGT1A1*28.

Four patients remained on study without progression of disease for more than 3 months. Of note is participant 4. Beginning 06/16/14 this participant had multiple previous treatments including CPT-11 in 2015/16. He was treated with PLX038 from December 2016 through July 2018 and had a confirmed partial response.

- 06/16/14- 07/23/14: FU/Xeloda/Docetaxel->CR
- 01/27-05/06/15: Herceptin/OxyPlt->SD
- 06/15-07/06/15: Xeloda->PD
- 10/13/15-6/29/16: Trastuzumab/FU/Irinotecan->SD
- 12/15/16- 07/2018: 387 mg/m^2 PLX038 (at 10/02/17-> 38% LN decrease, PR).

Table 4: Patient summaries

Pt. No.	Tumor Type	UGT Status	Date Enrolled	Dose Cohort	Dose Level	Date of first dose	Off-treatment/Off-study date	Months on therapy at Q3Wk	Reason off treatment
001-1	Rectal adenocarcinoma	Homozygous WT	4/15/2016	1	115 mg/m2	4/15/2016	7/7/2016	2.5	PD
001-2	GE adenocarcinoma	Homozygous WT	6/30/2016	2	172 mg/m2	6/30/2016	8/15/2016	1.5	PD
001-3	Rectal adenocarcinoma	Homozygous WT	10/18/2016	3	258 mg/m2	10/18/2016	11/29/2016	1.5	PD
001-4	Esophageal Adenocarcinoma	Homozygous WT	12/14/2016	4	387 mg/m2	1/3/2017	7/3/2018	18	PD
001-5	Adenocarcinoma of lower esophagus	Homozygous WT	12/7/2017	5	580 mg/m2	12/7/2017	12/15/2017	0.5	NE due to early death due to underlying tumor.
001-6	Gastric cancer	Heterozygous	4/12/2018	4	387 mg/m2	4/12/2018	5/24/2018	1.5	PD
001-7	Pancreatic cancer	Homozygous WT	4/23/2018	5	580 mg/m2	5/3/2018	6/8/2018	1	PD
001-8	Pancreatic cancer	Heterozygous	4/25/2018	4	387 mg/m2	5/9/2018	6/21/2018	1.5	PD

Pt. No.	Tumor Type	UGT Status	Date Enrolled	Dose Cohort	Dose Level	Date of first dose	Off-treatment/Off-study date	Months on therapy at Q3Wk	Reason off treatment
001-9	Colon cancer	Homozygous WT	8/14/2018	6	870 mg/m2	8/14/2018	9/24/2018	1.5	PD
001-10	Esophageal Adenocarcinoma	Homozygous WT	9/27/2018	7	1300 mg/m2	9/27/2018	1/10/2019	3.5	PD
001-11	Squamous cell of esophagus	Homozygous WT	11/26/2018	8	1730 mg/m2	11/26/2018	2/18/2019	2.5	PD
001-12		Homozygous *28						0	SF
001-13	Gastric adenocarcinoma	Heterozygous intermed met	1/11/2019	9	2300 mg/m2	1/17/2019	2/28/2019	1	PD
001-14	Esophageal Cancer	Heterozygous	3/12/2019	10	3060 mg/m2	3/14/2019	3/25/2019	0.5	Hospice
001-15	Esophageal Cancer	Heterozygous	4/2/2019	10	3060 mg/m2	4/15/2019	5/16/2019	1	Hospice
001-16	Esophageal Cancer	Heterozygous intermed met	5/16/2019	10	3060 mg/m2	5/16/2019	8/26/2019	3.5	PD
001-17	Esophageal Cancer	Heterozygous	5/30/2019	10	3060 mg/m2	6/3/2019	7/30/2019	2	Intercurrent illness
001-18	Gastric adenocarcinoma	Heterozygous intermed met	7/16/2019	10	3060 mg/m2	7/22/2019	8/14/2019	1	Unacceptable toxicity
001-19	adenocarcinoma	Homozygous WT	8/29/2019	10	3060 mg/m2	9/5/2019	11/7/2019	2	PD
001-20	adenocarcinoma	Homozygous WT	8/29/2019	10	3060 mg/m2	9/6/2019	10/18/2019	1.5	PI decision
001-21	Esophageal adenocarcinoma	Heterozygous	2/27/2020	11	2800 mg/m2	3/5/2020	4/16/2020	1.5	PD
001-22	Stomach adenocarcinoma	Heterozygous	3/12/2020	11	2800 mg/m2	3/16/2020	4/13/2020	1	PD
001-23	Esophageal adenocarcinoma	Heterozygous	8/27/2020	12	2600 mg/m2	8/31/2020	11/12/2020	2.5	PD
001-24	Colon cancer	Heterozygous	9/1/2020	12	2600 mg/m2	9/2/2020	8/7/2020	1	Intercurrent illness
001-25	Esophageal Cancer	Heterozygous	10/2/2020	12	2600 mg/m2	10/5/2020	1/20/2021	3.5	PD
001-26	Esophageal adenocarcinoma	Heterozygous	10/29/2020	12	2600 mg/m2	10/29/2020	12/7/2020	1.5	PI decision
001-27	Esophageal Cancer	Heterozygous	12/16/2020	12	2600 mg/m2	12/17/2020	1/5/2021	1	Unacceptable toxicity
001-28	solid tumor	Heterozygous *28	1/21/2021	12	2600 mg/m2			0	SF
001-29	metastatic adenocarcinoma	Heterozygous	2/24/2021	12	2600 mg/m2	2/25/2021	3/12/2021	0.5	Unacceptable toxicity
001-30	solid tumor	Heterozygous	4/2/2021	9	2300 mg/m2		3/10/2021	0	SF
001-31	solid tumor	Heterozygous	4/2/2021	9	2300 mg/m2	4/7/2021	4/19/2021	0.5	Death
001-32	solid tumor	Homozygous WT	7/16/2021	9	2300 mg/m2		7/29/2021	0	WOC/SF
001-33	gastric	Heterozygous *28	8/20/2021	9	2300 mg/m2	8/26/2021	9/8/2021	0.5	WOC
001-34	solid tumor		10/14/2021	13	2000 mg/m2	10/21/2021	11/11/2021	0.5	PI decision
001-35	solid tumor	Homozygous WT	11/3/2021	13	2000 mg/m2	11/11/2021	12/27/2021	1.5	PD
001-36	solid tumor	Heterozygous *6	11/17/2021	13	2000 mg/m2	11/18/2021	C3D15	on-study	
001-37	solid tumor	Heterozygous	2/3/2022	8	1730 mg/m2	2/3/2022	C1D2	on-study	
001-38	Solid tumor		2/9/2022	8	1730 mg/m2	2/10/2022		on-study	

Table 5. Possibly related adverse events

Possibly Related Adverse Events	# of Participants Affected N=16*	# of Participants with AEs, Highest CTCAE Grade	# of Participants with Serious AEs
Anorexia	12	Gr 1 (7), Gr 2 (4), Gr 3 (1)	0
Nausea	11	Gr 1 (6), Gr 2 (4), Gr 3 (1)	0
Vomiting	8	Gr 1 (6), Gr 2 (2)	0
Fatigue	8	Gr 1 (3), Gr 2 (2), Gr 3 (3)	0
Abdominal Pain	4	Gr 1 (1), Gr 2 (2), Gr 3 (1)	0
Hypokalemia	3	G1 (2), Gr 3 (1)	0
Neutropenia	1	Gr 2 (1)	0
Anemia	1	Gr 1 (1)	0
Hypocalcemia	1	Gr 2 (1)	0
Hyponatremia	1	Gr 1 (1)	0
Mucositis	1	Gr 1 (1)	0
Constipation	1	Gr 1 (1)	0
Ocular Pruritus	1	Gr 1 (1)	0
Loss of Appetite	1	Gr 1 (1)	0
Nasal Congestion	1	Gr 1 (1)	0
Rash	1	Gr 1 (1)	0
Small intestinal obstruction	1	Gr 3 (1)	1
Weight loss	1	Gr 2 (1)	0

* Patients may have experience more than 1 SAE

Table 6 shows pharmacokinetic (PK) parameters of various administered doses of Q3Wk PLX038 vs 350 mg/m^2 QWk CPT-11 and two other SN-38 prodrugs, Sacituzumab govitecan and Enz2208. Of note are the following:

- Most of the weight of PLX038 is due to the large 40 kDa PEG component; SN-38 content is only 3.5% of the total weight, and considering renal elimination of PLX038, the actual SN-38 present in vivo is only ~1% of the total weight.
- The MTD of pegamotecan, a related PEG-camptothecins analog was 7 g/m^2 [31] some 3-fold higher than the current dose of PLX038. We thus assume we could dose-escalate 3-fold higher than the current dose without PEG-related toxicity, if necessary, to reach MTD.
- At the current dose of 2.3 g/m^2, the free SN-38 is equivalent to the SN-38 formed from the MTD of Q3Wk CPT-11; but, Cmax is ~50% lower, $t_{1/2}$ is 10-fold longer, and AUC is over 5-fold higher. The PK benefits of PLX038 vs CPT-11 appear favorable.

Table 6. Human PK parameters of SN-38 from PLX038 vs other SN-38 prodrugs [A]

Total SN-38 [B]	Free SN-38 delivered [C]	SN-38 $t_{1/2}$	SN-38 C_{max}	SN-38 C_{14d} [D]	SN-38 AUC [E]
mg/m²/cycle	mg/m²/cycle	h (n)	nM (n)	nM	nM•h (n)
PLX038 Q3W					
14	4	97 ± 11.4 (4)	22 ± 6.2 (6)	1	1,660 ± 560 (4)
21	6	91 ± 3.7 (2)	14± 4.7 (3)	2	1,756 ± 1071 (2)
31	9	90 (1)	24± 13 (2)	3	2,513 (1)
46	13	85 hr	30	2	4,000
62	17	~100 hr	46	3	6,126
82	*23*	*~100 hr*	*68*	*8*	*11,356*
107	*32*	*118 ± 31 h*	*186 ± 88*	*11.7 ± 1.3*	*17,820 ± 2550*
CPT-11 Q3Wk [F]					
227	23	~12 hr	143		2,000
Sacituzumab govitecan ADC (QWk x 2, 3 wk. cycle) [32, 33]					
15	14	~20 hr	230	0.1	7,600
EZN-2208 (Q3W)					
10	10	30 h	370	~0	4,600

[A] PK data of 2,300 mg/m² not yet available; estimates were simulated from lower doses assuming $t_{1/2}$ = 100 h for PLX038 and dose linearity of Cmax.

[B] SN-38 ~3.5% by weight of PLX038.

[C] Delivered free SN-38 is ~ ~30% of total SN-38.

[D] C14d are estimated from given parameters (below LLOQ).

[E] AUC0-∞ values are calculated from the models.

[F] From label.

1.2.3 Rucaparib

Rucaparib is being developed as an antineoplastic agent. Nonclinical evaluation has demonstrated exquisite sensitivity of BRCA1 and BRCA2 homozygous mutant cell lines to rucaparib, which is attributed to PARP inhibition alone, and provides a rationale for the clinical assessment of

rucaparib as monotherapy in participants with hereditary (HRD) (germline) and acquired (somatic) deficiencies of BRCA1 and BRCA2. Clinical data indicate that benefit from treatment with a PARP inhibitor includes participants with a germline BRCA or somatic BRCA mutation and may extend to participants with other HRD alterations. This supports the investigation of PARP inhibitors such as rucaparib in a broader group of tumors with HRD (inclusive of BRCA and BRCA-like, as well other than BRCA mutations involved in HRD).

The first marketing authorization was granted in the United States (US) on 19 December 2016, for the treatment of patients with deleterious BRCA mutation (germline and/or -somatic) associated advanced ovarian cancer, who have been treated with 2 or more chemotherapies. Clovis voluntarily withdrew this indication in the US, Europe and GB in 2022 based on the detriment in overall survival (OS) observed for patients randomized to rucaparib versus chemotherapy.

Rucaparib is currently approved in the US for:

- The maintenance treatment of adult patients with recurrent epithelial ovarian (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) who are in response (complete or partial) to platinum-based chemotherapy.
- The treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen-receptor-directed therapy and a taxane-based chemotherapy.

The withdrawal of the treatment indication for BRCA-mutant ovarian cancer patients did not affect the other approved rucaparib indications.

For complete safety and efficacy information, refer to investigator brochure.

1.2.3.1 Overview of Clinical Findings

Phase 1, 2, and 3 clinical studies have or are being conducted to evaluate oral rucaparib in cancer participants. These studies have evaluated the PK (including the effect of food), metabolism, safety, and efficacy of rucaparib following oral administration at doses ranging from 40 mg QD to 840 mg BID in participants with solid tumors. Results from a Phase 1 dose-escalation study determined 600 mg BID as the RP2D, while an MTD was not identified. Phase 2 and Phase 3 clinical studies with oral rucaparib have been or are being conducted with the 600 mg BID dose and in participants with cancer associated with HRD.

1.2.3.2 Clinical Pharmacology

Assessment of rucaparib PK in cancer participants showed an approximate dose-proportional exposure after QD or BID dosing, rapid absorption with C_{max} achieved within 1.5 to 6 hours. The oral bioavailability was 36%. Rucaparib was moderately bound to human plasma proteins in vitro. At a dose of 600 mg BID rucaparib, steady state was achieved after approximately 1 week. At the target clinical dose of 600 mg, a high-fat meal increased the C_{max} and AUC_{0-24} of rucaparib by 20% and 38%, respectively, and delayed the median T_{max} by approximately 2.5 hours as compared with that under fasted conditions. The effect of food on rucaparib PK is not considered to be clinically significant, thus rucaparib can be taken with or without food.

Drug interactions with rucaparib as a substrate were assessed in a population PK analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultra-rapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyper inducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. Current smokers had

overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play limited role in rucaparib metabolism in vivo, and no rucaparib dose adjustment is needed when concomitantly administered with CYP inhibitors.

Concomitant treatment with proton pump inhibitors (PPIs) showed no clinically significant effect on rucaparib PK. No dose modification of rucaparib is required for participants who are receiving concomitant treatment with a PPI.

Results from Study CO-338-044 indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on P-glycoprotein (P-gp). Caution should be exercised in the concomitant use of drugs that are substrates of the above CYP enzymes with narrow therapeutic windows.

Results from the mass balance and metabolite profiling study CO-338-045 showed rucaparib excretion primarily in feces, followed by urine. M324 derived from oxidation of rucaparib was the major metabolite identified. Other metabolic pathways included N-demethylation, N-methylation, and glucuronidation. Plasma rucaparib showed a $T_{1/2}$ of 24 hours.

Preliminary PK data from prostate cancer participants (Study CO-338-052, TRITON2) are comparable with the data from ovarian cancer participants (Study CO-338-014, ARIEL3) suggesting a lack of PK difference between male and female participants.

1.2.3.3 Efficacy

The US approval of rucaparib for the treatment of women with relapsed BRCA-mutated (inclusive of germline and somatic BRCA mutations) ovarian cancer was based on pooled data for 106 participants enrolled in either Part 2A of Study CO-338-010 (n = 42) or Part 1 or Part 2 of Study CO-338-017 (ARIEL2) (n = 64) who met the following criteria: received at least 1 dose of rucaparib 600 mg; received at least 2 prior chemotherapy regimens, including at least 2 platinum-based regimens, and had a deleterious BRCA1/2 mutation (germline BRCA1/2 mutation in Study CO-338-010; germline or somatic BRCA1/2 mutation in Study CO-338-017 [ARIEL2]). In the integrated efficacy population, the investigator-assessed confirmed ORR per RECIST v1.1 was 53.8% (95% CI, 43.8-63.5), and the median duration of response was 9.2 months (range, 1.7-9.8; 95% CI, 6.6-11.6). For the secondary endpoint of investigator-assessed confirmed response per combined RECIST and GCIG CA-125 criteria, the ORR was 70.8% (95% CI, 61.1%-79.2%). Participants who were sensitive to their most recently administered platinum regimen had a higher ORR (65.8%; 95% CI, 54.3%-76.1%) than those who were resistant (ORR = 25.0%; 95% CI, 8.7%-49.1%) or refractory (ORR = 0%; 95% CI, 0.0-41.0%) to their most recent platinum regimen. The PFS rate at 6 and 12 months was 79.0% and 41.0%, respectively.

Rucaparib efficacy in the maintenance setting was demonstrated in 564 participants randomized in Study CO-338-014 (ARIEL3). Rucaparib maintenance treatment significantly improved PFS compared with placebo in all primary analysis groups of participants with recurrent ovarian carcinoma after a complete or partial response to platinum-based therapy. The median PFS in the BRCA population was 16.6 months (95% CI, 13.4-22.9) for the rucaparib-treated participants and 5.4 months (95% CI, 3.4-6.7) for the placebo group. The median PFS in the HRD population was 13.6 months (95% CI, 10.9-16.2) for rucaparib-treated participants and 5.4 months (95% CI, 5.1-5.6) for the placebo group. The median PFS in the intention to treat (ITT) population was 10.8 months (95% CI, 8.3-11.4) for the rucaparib group and 5.4 months (95% CI, 5.3-5.5) for the placebo group. Overall, rucaparib as maintenance treatment reduced the risk of progression by

63.5% (HR 0.365 [95% CI, 0.295-0.451]; p < 0.0001) in the ITT population, demonstrating a strong treatment effect over placebo. Analysis of non-nested, non-overlapping participant subpopulations indicate that the significant improvement in PFS observed in the ITT population was not driven only by the HRD or BRCA subpopulations. Nearly half (44.6%) of the participants in the rucaparib group showed benefit at 1 year compared to 8.8% in the placebo group. At 18 and 24 months, 32.0% and 26.0%, respectively, of participants who received rucaparib were still progression-free compared to 5.8% and 2.6% in the placebo group.

1.2.3.4 Safety

INTEGRATED SAFETY ANALYSIS FOR OVARIAN CANCER

Pooled safety data in the treatment setting are provided as of the 31 December 2017 visit cut-off for ovarian cancer participants in the ongoing Studies CO-338-010 (All Parts) and CO-338-017 (ARIEL2; both Parts 1 and 2), in which 565 participants with relapsed ovarian cancer received 600 mg BID rucaparib. Safety data in the maintenance setting are provided as of the 31 December 2017 visit cut-off for Study CO-338-014 (ARIEL3), in which a total of 561 participants have been treated (372 participants in the rucaparib group and 189 participants in the placebo group). Pooled safety data from the treatment setting as well as safety data in the maintenance setting are presented in **Table 7**.

Table 7: Incidence of TEAEs (All Causality; All Grades, Grade ≥ 3) Reported in ≥ 20% of Participants - Safety Population

Preferred Term	Treatment Setting Pooled Studies CO-338-010 and CO-338-017 (ARIEL2)[a]		Maintenance Setting Study CO-338-014 (ARIEL3)[b]			
	600 mg BID Rucaparib (N = 565) n (%)		600 mg BID Rucaparib (N = 372) n (%)		Placebo (N = 189) n (%)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Nausea	439 (77.7)	29 (5.1)	282 (75.8)	14 (3.8)	69 (36.5)	1 (0.5)
Asthenia/fatigue[c]	422 (74.7)	64 (11.3)	263 (70.7)	26 (7.0)	84 (44.4)	5 (2.6)
Vomiting	259 (45.8)	25 (4.4)	138 (37.1)	15 (4.0)	29 (15.3)	2 (1.1)
Anaemia/decreased hemoglobin[c]	250 (44.2)	137 (24.2)	145 (39.0)	80 (21.5)	10 (5.3)	1 (0.5)
ALT/AST increased[c]	223 (39.5)	61 (10.8)	129 (34.7)	38 (10.2)	8 (4.2)	0
Decreased appetite	219 (38.8)	16 (2.8)	88 (23.7)	3 (0.8)	26 (13.8)	0
Constipation	215 (38.1)	8 (1.4)	141 (37.9)	7 (1.9)	46 (24.3)	2 (1.1)
Dysgeusia	204 (36.1)	1 (0.2)	148 (39.8)	0	13 (6.9)	0
Abdominal pain	186 (32.9)	23 (4.1)	112 (30.1)	11 (3.0)	49 (25.9)	1 (0.5)
Diarrhoea	184 (32.6)	13 (2.3)	121 (32.5)	2 (0.5)	41 (21.7)	2 (1.1)
Thrombocytopenia/decreased platelets[c]	136 (24.1)	36 (6.4)	109 (29.3)	20 (5.4)	5 (2.6)	0
Dyspnoea	127 (22.5)	5 (0.9)	53 (14.2)	0	14 (7.4)	0
Blood creatinine increased	125 (22.1)	3 (0.5)	61 (16.4)	1 (0.3)	3 (1.6)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] The treatment setting pooled data presented are from the 31 December 2017 cut-off date for ovarian cancer patients in the ongoing Studies CO-338-010 (All Parts) and CO-338-017 (ARIEL2; both Parts 1 and 2).

[b] Safety data in the maintenance setting are provided as of the 31 December 2017 cut-off date for Study CO-338-014 (ARIEL3).

[c] Combined MedDRA preferred terms.

Note: Data are presented by decreasing frequency for TEAEs of all grades for the treatment setting pooled data.

In participants with ovarian cancer who received 600 mg BID rucaparib in pooled Studies CO-338-010 and CO-338-017 (treatment setting), as well as in Study CO-338-014 (maintenance setting), the most common TEAEs reported were primarily mild to moderate (Grade 1-2) in severity and include gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, decreased appetite, and dysgeusia. The most common TEAE ≥ Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased ANC, and asthenia/fatigue.

Effects on cardiac channel activity in vitro and a comprehensive assessment of the effects of rucaparib on ECG parameters in cancer participants demonstrated a low risk of cardiac effects by rucaparib.

The laboratory abnormalities reported in Study CO-338-014 (ARIEL3) were consistent with the TEAEs, with decreased hemoglobin, increased ALT, increased AST, and increased serum creatinine, most common in participants in the rucaparib group. Decreased platelets, neutrophils, leukocytes, lymphocytes, increased alkaline phosphatase and increased cholesterol were observed to a lesser extent.

ALT/AST elevations occurred early in treatment (i.e., by Day 1 of Cycle 2) and then resolved or stabilized over time. Treatment with rucaparib was continued at either the initial 600 mg BID dose or a lower dose. Elevations in ALT/AST were generally not accompanied by a concomitant elevation in bilirubin. Continued dosing with rucaparib in the presence of Grade 3 ALT/AST elevations is permitted if there are no other signs of liver toxicity.

Creatinine elevations were also observed early in treatment (i.e., by Day 1 of Cycle 2) and then stabilized with continued rucaparib treatment.

PRELIMINARY SAFETY ANALYSIS FOR PROSTATE CANCER

Safety data are provided as of the 06 March 2018 visit cut-off for prostate cancer participants in the ongoing Study CO-338-052 (TRITON2), in which 52 participants with mCRPC received 600 mg BID rucaparib. The safety profile of rucaparib in the mCRPC participant population is consistent with the safety profile in ovarian cancer participants. The most common TEAEs reported were primarily mild to moderate (Grade 1-2) in severity and include gastrointestinal toxicities (nausea, constipation, vomiting, diarrhea), asthenia/fatigue, decreased appetite, anemia/decreased hemoglobin, ALT/AST increased, and dizziness. The most common TEAEs ≥ Grade 3 include anemia/decreased hemoglobin, ALT/AST increased, thrombocytopenia/decreased platelets, nausea, and hypophosphatemia.

1.2.3.5 Efficacy and safety update

Studies CO-338-017 (ARIEL2) & CO-338-014 (ARIEL3)

The ARIEL program is evaluated rucaparib in patients with relapsed ovarian cancer. Study CO-338-017 (ARIEL2) was a 2-part, single-arm, open-label, Phase 2 study of rucaparib as treatment for relapsed high-grade ovarian cancer. The primary purpose of the study was to determine a molecular signature of HRD associated with a response to rucaparib in patients with relapsed disease. Efficacy data from Part 1 (n = 204 patients) indicated that rucaparib led to clinically meaningful and durable responses in patients whose tumor contained a BRCA1/2 mutation or HRD (BRCA-like molecular signature), demonstrating that benefit from PARP inhibitor treatment extended beyond patients with a BRCA mutation.

In Study CO-338-017, Part 2 (n = 287 patients), efficacy data in more heavily pretreated patients, predominantly with platinum-resistant/refractory disease, as compared to patients in Part 1, indicated the greatest activity in patients with a tBRCA mutation. However, there was greater activity in patients in Part 1 who had earlier-line platinum-sensitive disease as compared to the patients in Part 2 who were more heavily pretreated. The optimized molecular HRD signature from Study CO-338-017 was prospectively applied to the primary analysis of Study CO-338-014 (ARIEL3), an ongoing, randomized, double-blind, Phase 3 study of rucaparib versus placebo as switch maintenance treatment in patients with platinum-sensitive, relapsed, high-grade ovarian cancer (N = 564 enrolled patients).

Study CO-338-043 (ARIEL4)

Efficacy data indicated a highly statistically significant difference in invPFS between rucaparib and placebo for each of the 3 primary efficacy analysis populations (tBRCA, HRD, and ITT). The TEAEs reported with rucaparib treatment are consistent with those previously reported in open-label, non-randomized studies of rucaparib. The Phase 3 Study CO-338-043 (ARIEL4) evaluated rucaparib versus chemotherapy as treatment for patients with relapsed high-grade ovarian cancer associated with a deleterious BRCA1/2 mutation (N = 349 enrolled patients) and served as a confirmatory study for third-line+ treatment of BRCA-mutant ovarian cancer patients. Study CO-338-043 met the primary endpoint of invPFS, demonstrating a benefit for rucaparib treatment compared with active, standard-of-care chemotherapy. The safety profile was consistent with the safety profile in currently approved maintenance and treatment indications, and the tolerability of rucaparib was comparable with standard-of-care chemotherapy.

Final data analyses for Study CO-338-043 showed detrimental effect in terms of overall survival (OS) for patients randomized to rucaparib versus chemotherapy. The OS results were heavily confounded by a high rate of cross-over to rucaparib for patients initially randomized to the chemotherapy arm (close to 90% of all patients in ARIEL4 received rucaparib after randomization or crossover), as well as the post-progression subsequent treatments and was largely driven by patients with platinum-resistant disease.

Study CO-338-087 (ATHENA)

Study CO-338-087 (ATHENA) is an ongoing, randomized, double-blind, placebo-controlled Phase 3 study evaluating rucaparib as monotherapy (ATHENA-MONO) and in combination with nivolumab (vs. nivolumab; ATHENA-COMBO) as maintenance treatment following response to first-line platinum-based chemotherapy in patients with newly diagnosed ovarian cancer who have also undergone cytoreductive surgery.

TRITON Program

The TRITON program is evaluating rucaparib efficacy in a Phase 2 (CO-338-052 [TRITON2]) and a Phase 3 (CO-338-063 [TRITON3]) study of mCRPC. Study CO-338-052 (Phase 2) is evaluated rucaparib monotherapy for the treatment of mCRPC associated with evidence of HRD, with an emphasis on defects in BRCA1/2 and ATM genes, and an exploratory evaluation of other HRR gene mutations, in patients who have received prior AR-directed therapy and a taxane. Results from the final safety analysis of patients with mCRPC (n = 277) in Study CO-338-052 are consistent with those reported for ovarian cancer patients. Rucaparib PK exposure in prostate cancer patients is comparable to that in ovarian cancer patients (Study CO-338-014), suggesting no sex-related PK difference of rucaparib. Study CO-338-063 (Phase 3) is a randomized study

evaluating rucaparib monotherapy versus physician's choice (abiraterone acetate, enzalutamide, or docetaxel) for the treatment of mCRPC patients with a BRCA1/2 or ATM mutation who have received prior treatment with AR-directed therapy but have not yet received taxane-based chemotherapy in the castration-resistant setting. Additionally, a Phase 1b Study CO-338-107 (RAMP) is ongoing to evaluate the PK, safety, tolerability, and preliminary efficacy of rucaparib in combination with other anticancer therapies in patients with mCRPC.

Frequently reported TEAEs in the ovarian and prostate cancer populations included GI toxicities (eg, nausea and vomiting), myelosuppression, asthenia/fatigue, and elevated ALT/AST. These toxicities were successfully managed by treatment interruption or dose reduction and/or supportive care.

Study CO-338-010

Study CO-338-010 evaluated rucaparib in patients with any solid tumor that progressed on standard treatment (Part 1; Phase 1), patients with relapsed ovarian cancer associated with a BRCA mutation (Parts 2A and 2B; Phase 2), and patients with relapsed solid tumor and a BRCA mutation (Part 3; Phase 2). In Part 1, 56 patients with advanced solid tumors received oral rucaparib at dose levels of 40 mg to 500 mg QD and 240 mg to 840 mg BID. The PK of rucaparib was approximately dose-proportional in the tested dose range. In Parts 2A and 2B, clinically meaningful and durable responses to rucaparib were observed in patients with a gBRCA1/2 mutation. In Part 3 (Phase 2), the PK of a 300 mg dose strength tablet and a total dose of 600 mg rucaparib were characterized in patients with a solid tumor with a known deleterious BRCA1/2 mutation. The effect of food on rucaparib PK was also evaluated. At the target clinical dose of 600 mg, a high-fat meal increased the Cmax and AUC0-24 by approximately 20% and 38%, respectively, and delayed the median Tmax by approximately 2.5 hours. The effect of food on rucaparib exposure was not deemed clinically significant; rucaparib may be taken with or without food.

Study CO-338-081

Study CO-338-081 (RUCA-J) is an ongoing study. The Phase 1 study evaluated the safety and PK of rucaparib in patients with a previously treated solid tumor, to establish the RD in Japanese patients. The safety, tolerability, and PK of the RD in this study is being evaluated in Japanese patients who had progressed on standard treatment and had recurrent HGSOC (no gene mutation required), BRCA1/2-mutated breast cancer, or other solid tumor with evidence of a BRCA1/2 or other HRR gene mutation. At 600 mg BID, steady-state Cmax and AUC of rucaparib were slightly higher than that in Western patients, but the difference was not considered clinically significant, thus no adjustment in the starting dose is considered necessary.

Phase 1 Clinical Pharmacology Studies

Phase 1 clinical pharmacology studies were conducted in patients with advanced solid tumors. Results from the completed DDI portion (Part 1) of Study CO-338-044 indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and marginally inhibited P-gp. In Part I of Study CO-338-095 (a DDI study), rucaparib 600 mg BID caused 29% increase in Cmax and 35% increase in AUCinf of oral rosuvastatin (a BCRP substrate), and 43% and 56% increases in AUClast of the oral contraceptives ethinylestradiol and levonorgestrel, respectively. In Study CO-338-107, concomitant dosing of rucaparib with a strong CYP3A4 inducer enzalutamide showed no change in trough PK of either rucaparib or its metabolite M324 (formation is mediated by CYP3A4), indicating that CYP3A4

has no significant effect on rucaparib PK. Results from the completed mass balance and metabolite profiling portion (Part 1) of Study CO-338-045 following a single oral dose of [14C]-rucaparib showed that rucaparib was predominantly excreted in feces (71.9% of recovered 14C radioactivity), followed by urine (17.4% of recovered 14C radioactivity). Oxidation, N-demethylation, N-methylation, and glucuronidation were the major metabolic pathways for rucaparib, with M324, derived from oxidation of rucaparib, identified as the most abundant metabolite. In Study CO-338-078 (Part I), patients with moderate hepatic impairment showed similar Cmax but 44.6% higher AUCinf after a single oral dose of 600 mg rucaparib as compared to patients with normal hepatic function.

1.2.4 Rationale for this study

Top1 inhibitors are a class of chemotherapeutic agents that inhibit DNA replication and induce DNA strand breaks that require PARP for their repair. As such, PARP inhibition is highly synergistic in combination with Top1 Inhibitors [29]. In BRCA-wt participants, where PARP inhibitor monotherapy treatment does not demonstrate synthetic lethality, the ability to improve tumor response may be achieved with combination therapy. It is hypothesized that combining PARP inhibitors with Top1 inhibitors will result in increased efficacy in the clinic compared to either agent alone.

While the combination of PARP inhibitor and Top1 inhibitor is expected to be synergistic, dose-limiting toxicities have prevented this combination from being dosed at high doses of each drug, thereby limiting its potential clinical utility. The advantage of dosing with PLX038 compared to conventional Top1 inhibitor is the extended PK profile and prolonged local tumor exposure of SN-38. Since SN-38 is cleared more quickly from normal tissues than from tumor, it is hypothesized that delayed dosing of rucaparib (i.e. starting rucaparib dosing a few days after PLX038 administration) will allow for the expected window of maximum SN-38-induced toxicity to pass in the absence of concurrent rucaparib toxicity. However, the tumor levels of SN-38 are predicted to be sustained upon subsequent rucaparib dosing, therefore maintaining the ability of both drugs to act on tumor tissue simultaneously.

The primary hypothesis for the proposed study is that a tolerable combination of PLX038 plus rucaparib can be identified using a dose-escalation strategy that incorporates dose scheduling (i.e. intermittent dosing of rucaparib as opposed to continuous dosing).

The secondary hypothesis is that the combination of PLX038 plus rucaparib is more efficacious than either agent alone. The hypothesis that biomarkers will predict participant response to treatment will be investigated in an exploratory manner in two ways: markers of drug sensitivity and resistance will be measured pre-treatment, and pharmacodynamic markers will be measured post-treatment.

The starting dose of rucaparib (400 mg BID) is ~66% of its full dose (600 mg BID) and the starting dose of PLX038 (1,300 mg) is about 40% of its MTD (3,060 mg), a sufficiently low enough dose to ensure the safety as well as potential for enhanced efficacy. As discussed in the preclinical efficacy section of protocol **1.2.2.1** when used in combination with sub-therapeutic QD dose PARP inhibitor, talazoparib, a single low sub-therapeutic dose of PLX038A (10% of single dose) caused tumor shrinkage in TNBC xenograft models. Administering the PARP inhibitor with a 48 hour window after PLX038 will also likely minimize overlapping AEs of myelosuppression.

1.2.5 Rationale for Amendment to Change Dose-Escalation Strategy (Amendment Version Date: 03/19/2021)

Topoisomerase 1 inhibitors such as PLX038 damage DNA and are synergistic in combination with DNA damage response inhibitors (DDRi) such as PARP inhibitors including rucaparib; however, synergism is observed in both anti-tumor and toxic effects. Indeed, clinical trials of irinotecan and a PARPi inhibitor have shown both activity and toxicities and both drugs required significant dose reductions from their MTD [34-37]. Notably, in all such studies schedules were such that both DNA damaging agent and were PARPi concomitantly administered, so maximal systemic exposure of both drugs occurred concurrently and without tumor selectivity. One approach to achieve selective tumor inhibition involves an innovative "gapped-schedule" [38] (**Figure 3A**) and use of a tumor-targeted DNA damaging agent. Here, the tumor-targeted PLX038 is administered first, and allowed time (a "gap") to accumulate in the tumor and clear from the normal tissue. Then, rucaparib is introduced to prevent repair of DNA damaged by the SN-38 released from PLX038 entrapped in the tumor.

PLX038 is long-acting PEGylated prodrug of SN-38 (**Figure 1**), the active metabolite of irinotecan (CPT-11) and payload of the antibody drug conjugate (ADC) Troveldy which is a potent inhibitor of Topoisomerase 1 and causes DNA damage [30]. The nano carrier (NC) drug conjugate – designated PLX038 – is composed of a 4-arm 40 kDa PEG carrier containing SN-38 moieties attached to the ends of each arm. The prodrug slowly releases SN-38, and has long species-specific elimination $t_{1/2}$ values of ~20 hr in mice and ~5 days in humans. The 4-ARM PEG_{40kDa} provides a neutral, highly flexible, long half-life nanocarrier with a hydrodynamic diameter of about 15 nm, in accord with ideal properties proposed for nanocarrier tumor accumulation by EPR [39].

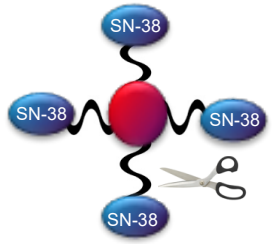

Figure 1. Depiction of PLX038, a slow releasing prodrug of SN-38.

The pharmacokinetics of ^{89}Zr-labeled surrogates of PLX038 in tumor xenografts and various normal tissues was studied by PET imaging (**Figure 2**)[40]. The observed concentration vs time profiles for normal tissues shows a high uptake at the earliest time of measurement, followed by an apparent monophasic loss and disappearance from the tissues. The nanocarrier is initially lower in tumors than in normal tissues because of poor vascularization of the tumor. The NCs in tumors then increases to a very high 10%–14% of the initial dose by approximately 4 days, with a $t_{1/2}$ of uptake of 2- to 3 days, associated with the long circulation time of the PEG conjugate and resultant high duration of tumor exposure to the conjugate. Then, the nanocarriers efflux from the tumor much more slowly than from other tissues, with $t_{1/2}$ values of 300- to 400 hours or up to 5-fold slower than from other tissues. *Importantly, at periods longer than approximately 3 days the PEG conjugates are at significantly higher concentration in tumor than in other tissues.* Using PLX038, it has been shown that within the tumor environment SN-38 is slowly released over periods of several weeks, substantially increasing tumor exposure to the active drug [41].

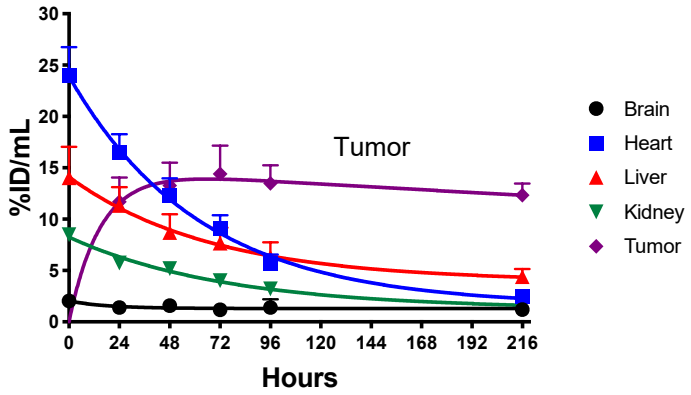

Figure 2. C vs t plot of accumulation of PLX038 surrogates in normal tissue and tumor [40].

Thus, the primary hypothesis of the study is that a tolerable combination of PLX038 plus rucaparib can be identified using a gapped schedule. The secondary hypothesis is that the combination of PLX038 plus rucaparib is more efficacious than either agent alone. If properly designed, the gapped-schedule ensures that when rucaparib is introduced, only the tumor would be exposed to both drugs, while normal tissues would be only exposed to the rucaparib. Clearly, the success of a gapped schedule will depend on a) achieving satisfactory tumor accumulation of both drugs, b) achieving the correct time gap between treatment with drug to achieve an optimal balance of efficacy and toxicity.

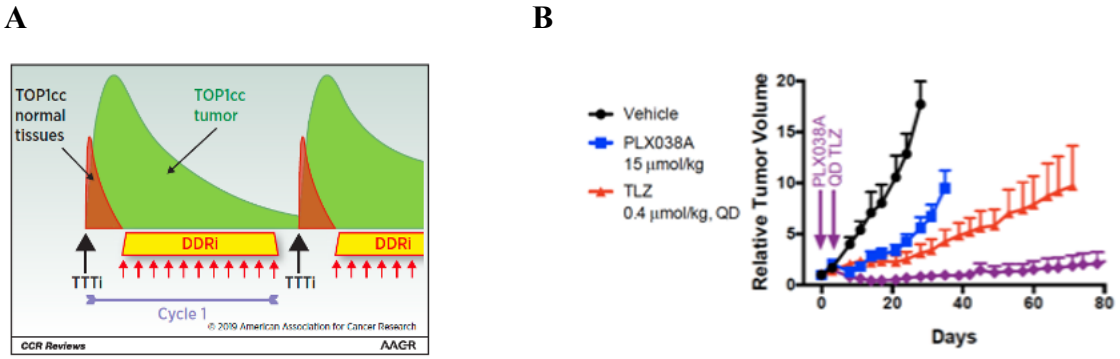

Figure 3. A) Rationale for gap-scheduling combination therapies with tumor-targeted topoisomerase 1 inhibitors (TTTi) such as PLX038 and DNA damage response inhibitors (DDRi, such as PARPi). The TTTi given on day 1 of each cycle initially produces DNA damage both in normal and tumor tissues (brown area). However, after a time gap, the TTTi is selectively retained and releases SN-38 predominantly in tumor tissues (green area). Treatment with the DDRi is then initiated (red arrows) while PLX038 is present in the tumor tissues but not in normal tissues. Such "gap-schedule" should avoid overlapping toxicity for normal tissues. B) Gap schedule dosing in MX-1 Xenograft BRCA1 deficient TNBC: PLX038 single dose; then 4 day washout (drug remains in tumor by enhance permeability retention (EPR)); then daily PARPi talazoparib.

Evidence for the success of gapped-scheduling has been obtained in preclinical models (**Figure 3B**). Here, a single dose of PLX038A (PLX038 modified to mimic human PK of PLX038 in the

mouse) followed a gap of 4 days to allow systemic clearance of the PLX038A, followed by daily PARPi causes complete tumor suppression without weight loss or change in blood counts; the remarkable efficacy was not seen with the same doses of either drug alone.

Data from dose level 1 demonstrates that PLX038A and rucaparib administered at 48-hour gap induces GI adverse events which precludes long-term administration of the combination, despite evidence of anti-tumor activity. The following modifications were considered to the dose escalation schema: a) dose lowering of the rucaparib (currently included in the protocol as dose level -1), or b) increase in the time-gap between dosing of PLX038 and the rucaparib. Dose lowering of rucaparib could reduce toxicity, but it may also reduce efficacy; increase in the time-gap between dosing could retain efficacy but reduce toxicity. We believe there are good justifications for either approach.

There are several reasons why an increased gap may be preferable to dose modifications:

1. *The current gap may not be optimal for tumor accumulation of PLX038.* In rodent models, the t_{max} for tumor accumulation of PLX038 is ~100 hrs [40]. If similar in humans, the 48 hr gap may not be sufficient to allow maximal tumor uptake to take maximum advantage of the highest tumor/systemic PLX038 before BID rucaparib dosing is initiated.
2. *The efflux of PLX038 from xenograft tumors is extremely slow compared to normal tissues, so an increased gap time may not affect efficacy (tumor retention of PLX038) but could reduce toxicity (reduced drug in tox target tissue).* The relative accumulation and efflux rates of PLX038 from human clinical tumors is unknown, however the underlying factors responsible for accumulation/slow efflux in xenografts (i.e. increased vasculature pore size, poor lymphatics, high interstitial pressure) are present in all solid tumors. In the absence of targeted uptake, tumor accumulation is driven by the concentration of PLX038 in the blood, with the maximum tumor concentration being determined by the ratio of influx/efflux rates; lowering the administered dose will lower the absolute concentration of PLX038 in the tumor and thus decrease antitumor activity. Given the slow efflux from the tumor relative to clearance from the systemic circulation, however, increasing the gap between administration is expected to have minimal effect on the intratumoral level of PLX038 while more significantly lowering the level of PLX038 in non-target tissues at the onset of PARPi dosing. This argues that the dose of PLX038 should remain at its current level, or be increased if possible, while increasing the delay between administration of PLX038 and PARPi.
3. *The PK for SN-38 released from PLX038 in the human shows a $t_{1/2}$ = 120 h, so increasing the gap from 2 to 5 days should not greatly affect tumor exposure but significantly reduce systemic exposure.* The systemic SN-38 at the current gap of 48 hr is 76% of the ~55 nM C_{max}, while at a gap of 120 h (5 days) the systemic SN-38 would be decreased to 50% of C_{max} (or ~27 nM). While the tumor accumulation of PLX038 will remain unchanged due to the invariant dose and slow exit from the tumor, the systemic level of SN-38 at the time the PARPi is introduced will be reduced ~1.5-fold upon changing from a 2 to 5 day gap schedule. This is anticipated to reduce systemic toxicity with less effect on antitumor efficacy.
4. *The current gap may not be sufficient to allow optimal elimination of PLX038 from toxicity target organs (e.g. intestinal epithelial cells) by the time PARPi is administered.* Unlike the SN-38 formed from CPT-11 which shows high liver/GI-exposure (as evident from high SN-38G/SN-38), the SN-38 from PLX038 has very low liver/GI exposure (as evident from low SN-38G/SN-38) [30, 42]; indeed, at the dose of PLX038 used in the NCI trial, SN-38G is

barely detectable. Nevertheless, GI exposure to SN-38 released from PLX038 may contribute to the GI toxicity observed with rucaparib. As with SN-38, SN-38G from PLX038 in the human shows a $t_{1/2}$ = 120 h. Hence, the GI exposure to SN-38 would be reduced ~2-fold upon changing from a 2- to 5 day gap schedule which should reduce GI toxicity.

5. *Dose reductions of rucaparib have not had an impact on GI adverse effects.* Symptoms persisted despite reductions in all who required dose reductions.

Based on the above considerations, the following dose levels were proposed (no longer applicable as of amendment version date 4/8/2022):

Dose level	PLX038 every 3 weeks, g/m2 IV	Rucaparib, mg PO BID
Former dose level 1 (completed)	1.3	400 mg, days 3-19
-1A	1.0	300mg, days 5-19
1A	1.3	300mg, days 5-19
2A	1.3	400mg, days 5-19
3A	1.3	600mg, days 5-19

1.2.6 Additional Summary Safety and Efficacy Results and Rationale for Further Changes to Dose Escalation Strategy (as of amendment version date: 04/08/2022)

A total of 8 patients were enrolled at dose level 1 [PLX038 1,300 mg/m2 (~50% MTD) and rucaparib 400 mg BID (66% recommended dose)] with a 48-hour window between PLX038 and rucaparib. Six of 8 patients are evaluable for DLT-assessment. One of six evaluable patients had hematologic DLT of febrile neutropenia, grade 4 thrombocytopenia, and inability to begin subsequent treatment in 21 days due to drug toxicity. Seven patients had non-DLT GI toxicity (most commonly abdominal discomfort, diarrhea, or nausea). In six cases, these symptoms required rucaparib dose reductions or interruptions. In general, these symptoms persisted after rucaparib dose reduction to 300 mg, and to 200 mg in one case.

Of seven patients evaluable for efficacy, there were 3 progressive disease (PD), 2 stable disease (SD), 1 partial response (PR), and 1 complete response (CR). Of the two evaluable patients with known tumor homologous recombination deficiencies, there were 1 CR (ATM mutated breast adenocarcinoma, **Figure 4**) and 1 PR (germline TP53 and somatic BRCA1 mutated triple negative breast cancer, **Figure 5**), and both patients remained on treatment for 11.5 and 4.5 months respectively. Notably, the responding patients had previously progressed on topoisomerase and PARP inhibitors. Minor responses qualifying as RECIST stable disease were seen in two other patients.

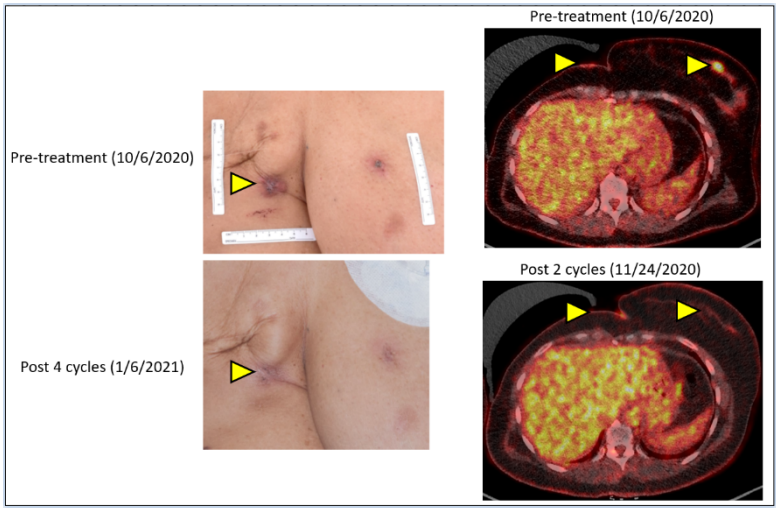

Figure 4. Complete response in patient with ATM mutated breast adenocarcinoma and multiple prior therapies.

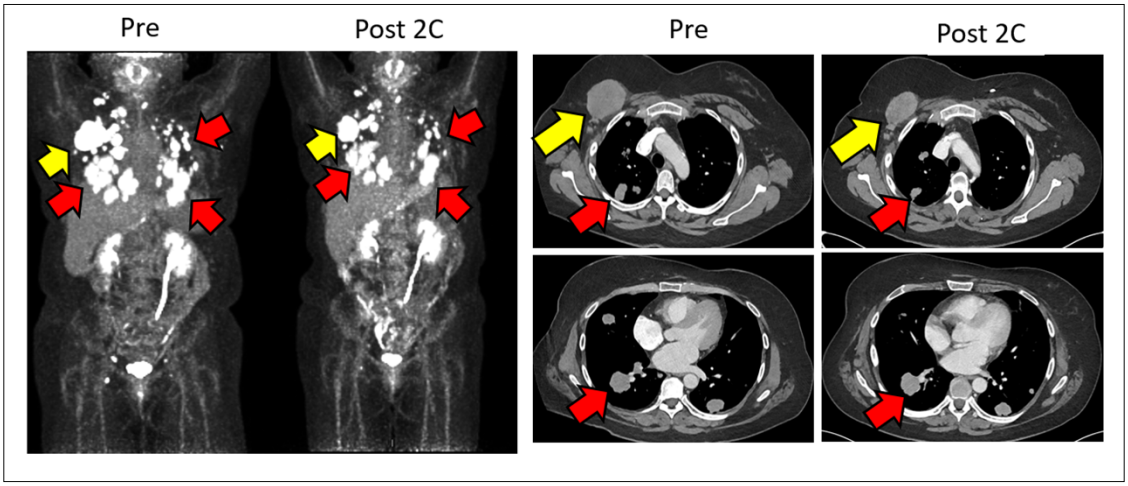

Figure 5. Tumor response (stable disease by RECIST -18%) in patient with germline TP53 and somatic BRCA1 mutated TNBC.

In summary, data from dose level one demonstrated that, while there are clear signs of efficacy, several patients had intolerable GI toxicities, none of which have met the criteria for DLT. Based on a number of considerations (outlined in more detail in section **1.2.5**), the protocol was amended to decrease the starting dose of rucaparib to 300 mg BID (dose level 1A) and increase the gap to 5 days between PLX038 and rucaparib (amendment version 3/19/2021).

Two subjects enrolled at new dose level 1A. Both subjects developed febrile neutropenia and enterocolitis related to both PLX038 and rucaparib and died (reported to the IRB as unanticipated Problems REF 563724 & 564323). A patient died likely due to neutropenic sepsis related to PLX038 and rucaparib and another patient's death was likely due to disease progression in the setting of neutropenic enterocolitis, related to study drugs. Both rucaparib and PLX038 are known

to be associated with neutropenia and infection. While neutropenic sepsis leading to death is an expected AE with the class of TOP1 inhibitors (such as SN38), these events are considered as unexpected for PLX038 from a regulatory perspective as they had not been previously reported with PLX038.

Samples for PLX038 pharmacokinetic analysis were drawn on Cycle 1 day 1 (C1D1) at the following time points: before PLX038 infusion, end of infusion (EOI) (+5 minutes), 2 (+/- 15 minutes) hours, 4 (+/- 15 minutes) hours and 24 (+/- 30 minutes) hours post EOI, on C1D5 just before starting rucaparib, and on C2D1 before the next PLX038 infusion. Samples for rucaparib analysis were collected on C1D7 (optional): before rucaparib, 2 hours (+/- 15 minutes), 3 hours (+/- 15 minutes), 4 hours (+/- 15 minutes) and 24 hours (+/- 1 hour) post rucaparib dosing. Samples were also collected on day 1 of all subsequent cycles before PLX038 dosing.

There were 9 patients enrolled with sufficient PK data for inclusion in this analysis. Sparse sampling of rucaparib precluded a full-time course of concentration data needed to calculate most PK parameters. However, pre-dose (trough) concentrations at steady state (C1D8 and beyond) were analyzed by dose and compared to literature. While no proper statistical comparisons could be made, it appears rucaparib trough concentrations in this study were reasonably consistent with prior data (**Figure 6**).

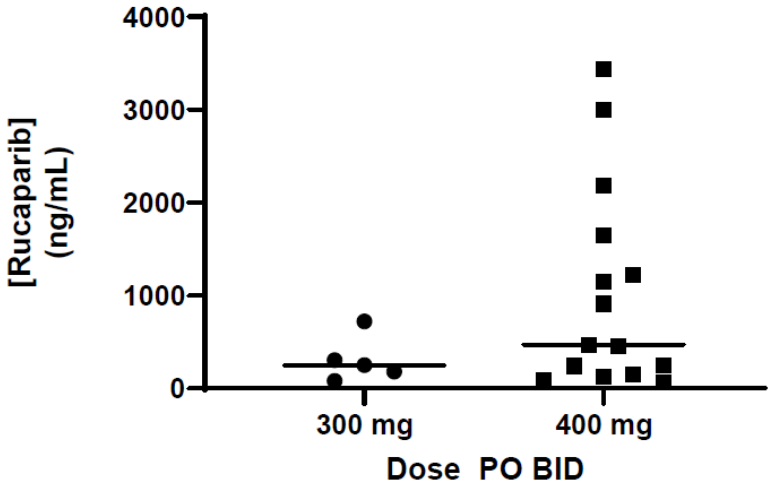

Figure 6. Comparison of Steady-State Troughs (Pre-dose) of 300 mg or 400 mg Rucaparib given Orally Twice Daily.

The total plasma concentrations of SN38 and its UGT1A1-catalyzed metabolite, SN38-G, were measured in all evaluable patients (**Figure 7**). PLX038 was designed to prolong the half-life in humans (expected 120 hr [2]), and the observed half-life was consistent with this expected value. There were nanomolar levels of SN38, indicating minimal ex vivo release of SN38 from PLX038. The median metabolite: parent ratio of SN38-G to SN38 was 0.29, similar to literature [3]. There was insufficient PK data on subsequent cycles to assess accumulation on the q3wk schedule, or whether there was a drug interaction with rucaparib PO BID. However, both the patients at dose level 1A (patients #9 and #10) who developed neutropenic enterocolitis had elevated levels of SN38G compared to the other patients (**Figure 8**). We saw no genotype effect of UGT1A1*28 on SN38 or SN38-G exposures.

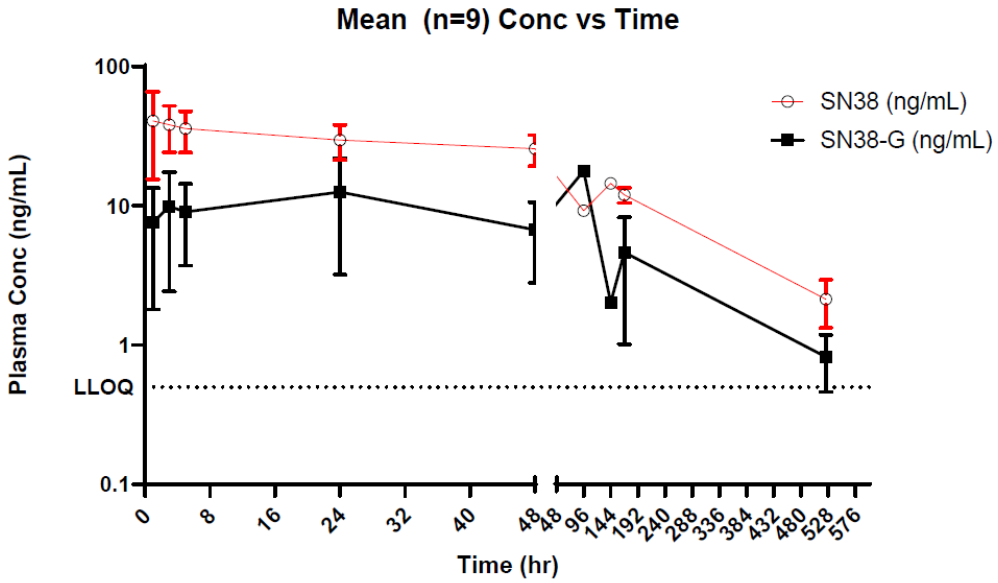

Figure 7. Mean First Dose PLX038 (1 g/m2) Plasma Concentration vs Time Profile.

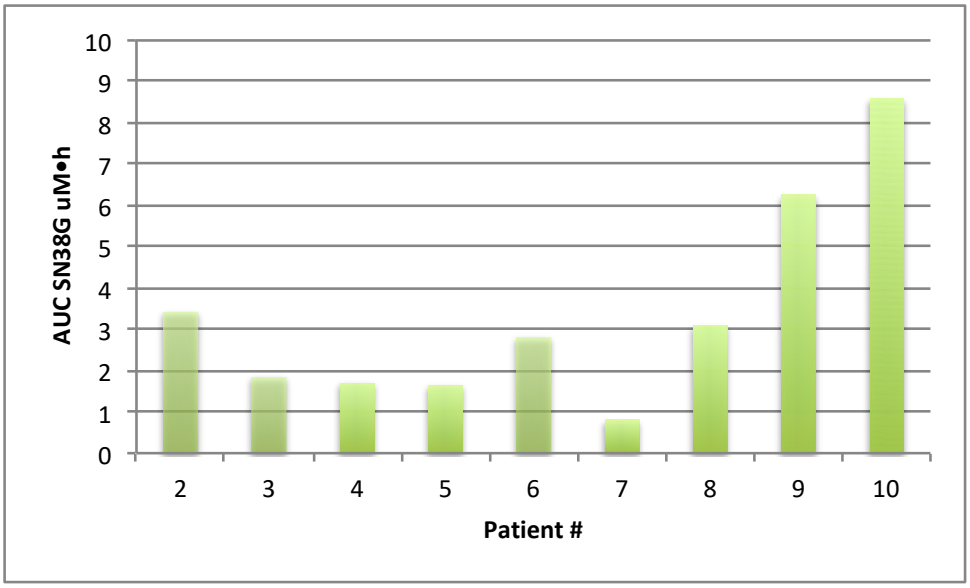

Figure 8. SN38-G AUC by Patient.

In summary, there were early signs of promising efficacy, but associated with intolerable GI toxicity at dose level 1, which prompted amendment of the protocol to reduce the dose of rucaparib and increase the gap between PLX038 and rucaparib. The first two patients treated with the 5-day gap (dose level 1A) developed drug-related neutropenic enterocolitis. Both rucaparib and PLX038 are known to be associated with neutropenia and infection. While neutropenic sepsis leading to death is an expected AE with the class of TOP1 inhibitors (such as SN38), these events are considered as unexpected for PLX038 from a regulatory perspective as they had not previously been reported with PLX038. Thus, new risks from the combination have been uncovered during the course of the study, but given the patient population being studied – with resistant cancer and no other standard options, and the early responses observed, the combination might still be of

potential benefit. The following considerations were discussed with drug manufacturers Clovis and Prolynx, and experts in the field with the goal of minimizing risk:

- The eligibility criteria were revised to include patients who have exhausted all approved standard options.
- Individual patients will be observed for at least four weeks in the dose escalation phase before the next patient can be enrolled.
- It is unlikely that an insufficient end-gap (gap between last dose of rucaparib and next dose of PLX038) contributed to the toxicities. Patient #9 had a 100-hour gap between last dose of rucaparib and cycle 2 PLX038 due to scheduling/logistical issues, doubled the prescribed 48-hour gap. Patient #10 had a 11-day gap since he stopped rucaparib early due to diarrhea and urinary infection.
- It is unlikely that excluding patients with heterozygous for UGT1A1*28 would help reduce toxicity. UGT1A1 is a hepatic enzyme that metabolizes SN38 to SN38-G. It is a polymorphic enzyme and UGT1A1*28, is often assessed for genotype. We found no genotype effect of UGT1A1*28 on SN38 or SN38-G exposures, and specifically patients 9 and 10 were heterozygous for UGT1A1*28. The low SN38-G to SN38 ratio suggests sufficient UGT1A1 activity in patients treated thus far. The current standard of care does not require dose reduction of irinotecan in UGT1A1 heterozygotes, who are clinically much closer to homozygous wild type in terms of irinotecan safety than to homozygous mutant patients. Accordingly, the frequency of grade 3/4 neutropenia among patients treated with sacituzumab Govitecan, an antibody–drug conjugate with SN-38 payload were 67% in patients homozygous for the UGT1A1 *28 allele and 46% each in patients heterozygous for the UGT1A1*28 and homozygous for the wild-type allele.
- Reducing the dose (calculated as g/m2) and capping the total dose of PLX038 may reduce the incidence of severe toxicities. Patient #9 received more than 3000 mg based on body surface area (**Table 8**). Other patients in the trial received doses of 2700 mg or lower including patient #10. In the phase I study of PLX038 monotherapy, the frequency and severity of diarrhea was higher among patients who received higher doses, especially at 1300 mg/m2 or higher.
- Primary prophylactic G-CSF will decrease incidence of neutropenic events. Due to the potential for G-CSF to stimulate neutrophil precursors at the same time as myelosuppression from chemotherapy, it is recommended that G-CSF be administered 24 hours after chemo administration. In addition, several studies have showed that use of G-CSF on the same day as chemo may result in worse neutropenic outcomes [43]. While the timing of G-CSF is a concern given the extended tissue accumulation of PLX038, all 3 patients who received G-CSF on study (patients #1, 7 and 8) have had appropriate increases in neutrophil counts. However, G-CSF will be administered at least 72-hours after PLX038 given this theoretical risk.

Table 8. Cumulative PLX038 cycle 1 dosing

Patient	Cumulative PLX038 dose in cycle 1, mg
1010001	2040
1010002	2171
1010003	2366

1010004	1870
1010005	2150
1010006	2700
1010007	2510
1010008	2030
1010009	3110
1010010	2310

Based on the above considerations, the following dose levels are proposed going forward.

Dose level	**PLX038 every 3 weeks, IV**	**Rucaparib, PO BID**
Former dose level 1 (completed)	1.3 g/m2	400 mg, days 3-19
Former dose level 1A (completed)	1.3 g/m2	300mg, days 5-19
1B	580 mg/m2	300mg, days 6-19
2B	870 mg/m2	300mg, days 6-19
3B	1000 mg/m2	300mg, days 6-19

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

- Subjects with:
  - histologically confirmed solid tumors (Phase I)

    OR
  - histologically or cytologically confirmed SCLC (Phase II)

    OR
  - histologically or cytologically confirmed extra-pulmonary small cell carcinomas (Phase II)
- Age ≥18 years. Because no dosing or adverse event data are currently available on the use of PLX038 in combination with rucaparib in participants <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
- Subjects must have progressed on or after standard first-line systemic chemotherapy and have no effective treatment options.
- Participants must have disease that is not amenable to potentially curative resection.
- Participants must have measurable disease per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease.
- Participants with asymptomatic brain metastases and treated brain metastases are eligible.
- ECOG performance status ≤ 2 (**Appendix A**).

- Adequate hematological function defined by:
  - white blood cell (WBC) count ≥ 3 × 10^9/L,
  - absolute neutrophil count (ANC) ≥ 1.5 ×10^9/L,
  - platelet count ≥100 × 10^9/L,
  - Hgb ≥9 g/ dL
- Adequate hepatic function defined by:
  - a total bilirubin level ≤ 1.5 × ULN,
  - an AST level≤2.5×ULN, (≤ 5X ULN if liver metastasis)
  - an ALT level ≤2.5 ×ULN, (≤ 5X ULN if liver metastasis).
- Adequate renal function defined by:

Creatinine OR Measured or calculated creatinine clearance (CrCl) (eGFR may also be used in place of CrCl) [A]	< 1.5x institution upper limit of normal OR ≥ 45 mL/min/1.73 m^2 for participant with creatinine levels ≥ 1.5 X institutional ULN
[A] Creatinine clearance (CrCl) or eGFR should be calculated per institutional standard.	

- The effects of the study treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study treatment and up to 6 months after the last dose of the study drug (s). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Subjects must be able to understand and willing to sign a written informed consent document.

2.1.2 Exclusion Criteria

- Participants who are receiving any other investigational agents.
- Systemic anti-cancer treatment or major surgery within 2 weeks prior to enrollment.
- Radiotherapy within 24 hours prior to enrollment.
- Participants who require treatment with strong inhibitors or inducers of CYP3A or with UGT1A1 inhibitors during the planned period of investigational treatment with PLX038.
- Participants with known Gilbert's syndrome.
- Participants homozygous for the UGT1A1*28 variant allele with severely reduced UGT1A1 activity.

- Participants with known HIV, HCV, HBV status on antiviral drugs are excluded due to the absence of previous experience with concurrent use of antiviral medications and the investigational drug product to be evaluated in the current study and possible for adverse pharmacokinetic and/or pharmacodynamic interactions.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to PLX038 or rucaparib.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that may impair the participant's tolerance of study treatments.
- Pregnant women are excluded from this study because PEGSN38 and rucaparib potential for teratogenic or abortifacient effects are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with PEGSN38 and rucaparib, breastfeeding should be discontinued if the mother is treated with study drugs.

2.1.3 Recruitment Strategies

This study will be posted on the CCR website, www.clinicaltrials.gov and on NIH social media forums. Outside providers and colleagues may directly refer participants for screening into this study.

2.2 Screening Evaluation

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for study #01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols). Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

Within 14 days prior to treatment unless otherwise noted below:

- Complete medical history and physical examination, including height, weight, vital signs, and ECOG performance status.

- EKG
- Laboratory Evaluation
    - Hematological profile: CBC with differential and platelet count;
    - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid;
    - PT/PTT;
    - Cholesterol (fasting);
    - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy) (7 days prior to treatment);
    - Urinalysis
    - Blood or buccal test for defining of UGT1A1 status by polymerase chain reaction (PCR) (any time prior to enrollment, outside test results are acceptable)
- CT/MRI of chest, abdomen and pelvis;
- Brain MRI (if clinically indicated);
- Tumor evaluation / tumor measurements;
- Histologic or cytologic confirmation from any certified laboratory (at any time point prior to enrollment). If there is no available documentation, biopsy will be performed to confirm the diagnosis.

2.3 Participant Registration and Status Update Procedures

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	**Name**	**Description**
1	Phase I	Subjects with solid tumors enrolled to PLX038 and rucaparib escalation dose levels.
2	Phase IIA	Subjects with SCLC enrolled at the MTD of PLX038 and rucaparib after the MTD of PLX038 and rucaparib is established.
3	Phase IIB	Subjects with extra-pulmonary small cell carcinomas enrolled at the MTD of PLX038 and rucaparib after the MTD of PLX038 and rucaparib is established.

Arms

Number	Name	Description
1	Arm 1	Escalating doses of PLX038 and rucaparib
2	Arm 2	MTD of PLX038 and rucaparib

Arm assignment

Subjects in cohort 1 will be directly assigned to Arm 1.

Subjects in cohorts 2 and 3 will be directly assigned to Arm 2.

2.4 Baseline Evaluation

Tests done at screening do not need to be repeated on baseline if performed in designated time frame prior to start of study treatment.

Within 14 days prior to first dose:

- CT/MRI of chest, abdomen and pelvis
- Tumor evaluation / measurements
- Optional tumor research biopsy
- Baseline symptoms evaluation
- Concomitant medication
- Collection of available unstained slides or a block from previous biopsies/surgeries for research

3 STUDY IMPLEMENTATION

3.1 Study Design

This is an open label Phase I/II trial, accruing initially one cohort to determine maximum tolerated dose (MTD) of combined treatment of PLX038 and rucaparib (Phase I); and to examine safety and efficacy of the PLX038 in combination with rucaparib in the following cohorts (Phase IIA and IIB).

Up to 3 dose levels of combined treatment of PLX038 and rucaparib will be tested in Phase I (**Table 9**) with up to 18 subjects enrolled in addition to the 8 participants treated prior to amendment version 03/19/2021. Once an MTD of combined treatment of PLX038 and rucaparib has been determined, up to 35 subjects may be evaluated at MTD in the Phase II cohorts, inclusive of those participants treated at the MTD during the Phase I if they are eligible for the phase II evaluation.

Participants will receive treatment in cycles consisting of 21 (+7) days.

Administration of PLX038 will be every 3 weeks by IV infusion starting on day 1 of cycle 1. Granulocyte-colony stimulating factors (G-CSF) should not be used within at least 24 hours of PLX038 administration. Outside of this restriction window, G-CSF may be administered as clinically indicated.

Rucaparib will be administered on days 6 to 19 of a 21-day cycle starting at 300 mg PO BID.

Treatment with PLX038 and rucaparib will continue until participant meets off treatment criteria (Section **3.7.1**).

Granulocyte-colony stimulating factors (G-CSF) will be given prophylactically in each cycle to prevent/treat neutropenia (for both phase 1 and phase 2). G-CSF will be administered at least 72-hours after PLX038 in each cycle, with at least 14 days elapsing until the next planned chemotherapy dose.

Optional biopsies may be performed at: baseline, on day 4 or 6 of Cycle 1 (prior to rucaparib dosing) and between days 7 and 14 of Cycle 1.

Participants may be admitted for cycle 1 as there are PK studies planned to be performed.

3.1.1 Dose Limiting Toxicity

The DLT period is one cycle, 21 days.

The following events will be considered DLTs if deemed drug-related (CTCAE v5.0):

- Grade 3 or 4 neutropenia complicated by fever ≥ 38.5°C (i.e. febrile neutropenia) and/or documented infection;
- Grade 4 neutropenia that does not resolve within 7 days
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia complicated with hemorrhage;
- Grade 4 anemia that does not resolve within 7 days despite optimal therapy;
- Inability to begin subsequent treatment course within 21 days of the scheduled date, due to study drug toxicity;
- Any grade 3 non-hematologic toxicity with the following exceptions
    - fatigue/asthenia lasting less than 2 weeks in duration
    - mucositis in subjects who have not received optimal therapy for mucositis
    - vomiting or diarrhea lasting less than 72 hours whether treated with an optimal anti-emetic or anti-diarrheal regimen or not
    - alkaline phosphatase changes

3.1.2 Phase I Cohort

Dose escalation will follow the classical '3+3' trial design by Fibonacci sequence with dose levels defined in **Table 9**.

Starting dose level is Dose level 1B.

If none of the first three participants in a Dose level group experiences a dose-limiting toxicity during the DLT period, another three participants will be treated at the next highest dose level. However, if one of the first three participants experiences a dose-limiting toxicity during DLT period, three more participants will be treated at the same dose level. Dose escalation continues until the final dose level meets safety criteria (< 2 DLTs in 6 participants during DLT period) or at least two participants among a Dose level group of three to six participants experience dose-limiting toxicities.

Note: If there are ≥2 DLTs in the Dose level 1B, we will consider amending the study with new dose levels.

Table 9. Dosing schedule of PEGSN38 and rucaparib.

Dose level	PLX038 every 3 weeks, IV	Rucaparib, PO BID
Former dose level 1 (completed)	1.3 g/m2	400 mg, days 3-19
Former dose level 1A (completed)	1.3 g/m2	300mg, days 5-19
1B	580 mg/m2	300mg, days 6-19
2B	870 mg/m2	300mg, days 6-19
3B	1000 mg/m2	300mg, days 6-19

PLX038 dose will be capped at 2000 mg total dose.

G-CSF will be administered at least 72-hours after PLX038 in each cycle.

The MTD is the dose level at which no more than 1 of 6 participants experience DLT during the DLT evaluation period, and the dose below that at which at least 2 (of 6) participants have DLT as a result of the drug.

Every subject in each dose level group of the safety run-in will be observed for at least 4 weeks after first dose of PLX038 before the subsequent subject can be treated.

Subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced and not included in the DLT evaluation.

Intra-participant PLX038 and rucaparib dose escalation or de-escalation are not permitted for subjects enrolled in the Phase I during the DLT finding period.

In case of DLT definitely attributed to one of the study drugs, participant will be taken off this drug and per PI discretion may continue treatment with the other drug alone.

Participant will be eligible for the DLT evaluation if at least ≥85 percent of rucaparib scheduled doses were taken within the DLT period.

3.1.3 Phase II Cohorts

The safety and efficacy evaluation of the combination will continue during Phase II with the PLX038 and rucaparib MTD identified during phase I.

We will initially enroll 16 evaluable subjects into cohort Phase IIA (inclusive of those participants with SCLC treated at the MTD during the safety run-in). If 2 or more of the first 16 subjects have clinical benefit, then accrual would continue to a total of 25 subjects. If less than 2 subjects have clinical benefit, enrollment into this cohort will be closed.

Simultaneously with enrollment of participants into cohort Phase IIA, up to 10 participants with extrapulmonary small cell cancers may be enrolled into cohort Phase IIB. CBR of these participants will not be included in the primary statistical analysis and will be described in an exploratory manner.

Enrollment into phase II part of the study can commence after DLT period of 6^{th} subject of respective Dose level group is complete.

3.2 Study Stopping Rules

For safety reasons, enrollment will be temporarily halted until an expedited safety report is sent to and reviewed by the FDA and the SAE has been evaluated by the investigators for grade 5 toxicity attributable to treatment regimen occurring within 30 days of receiving investigational agents.

The stopping rule has been met with two patients having grade 5 events at dose level 1A, but will be applicable to future subjects who enroll.

3.3 Drug Administration

3.3.1 PLX038

PLX038 will be administered as a 1-hour (-10 minutes / +30 minutes) IV infusion on Day 1 of each cycle (21 days).

PLX038 vials (220 mg/vial) should be brought to room temperature before use. However, the final diluted product should ideally be used as soon as possible.

Vital signs will be collected within 1 hour before PLX038 infusions, at least once during the infusions, and within 30 minutes after the completion of the infusion.

To calculate the dosage, height measured at screening and weight measured at day 1 of current cycle will be used.

3.3.2 Rucaparib

Rucaparib will be given orally at designated dose twice a day on days 6 to 19 of every 21-day cycle. There should be a minimum 5 day window between PLX038 and rucaparib.

Rucaparib should be taken at approximately the same times each day. Doses should be taken within 2 hours of the scheduled time.

In case of a missed dose (more than 2 hours late) or vomiting after taking rucaparib, participants will be instructed not to make up the missed dose.

Missing of 15% of the doses for any given cycle is allowed.

Participants will be recommended to have 8 mg of ondansetron taken with small meal or snack to prevent nausea and vomiting approximately 30 minutes prior to each dose of rucaparib**.**

Participants will complete and return Participant's Diary (**Appendix B**).

3.4 Dose Delay or Modifications

In case of toxicity as defined below definitely attributed to one of the study drugs, participant will be taken off this drug and per PI discretion may continue treatment with another drug only.

For participants who are on combination therapy and benefiting from treatment, since we don't know which agent is driving the response (i.e. either of the drugs alone or the combination), in the event that one drug is causing toxicities and has to be discontinued, it is reasonable to continue the other drug to see if the participant might benefit from it.

3.4.1 Phase I during evaluation period

See Section **3.1.2**.

3.4.2 Phase I after DLT evaluation period and Phase II

When, at the beginning of a treatment cycle, treatment delay related to PLX038 is indicated, treatment with rucaparib must be delayed too. There should be a minimum 48-hour window between PLX038 and rucaparib.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one drug, the dose of another drug does not require modification.

The dose of PLX038 and rucaparib may be reduced for toxicity using the following guidelines depending on the toxicities (and drug deemed to be responsible for toxicity) observed.

Table 10: Dose reductions for rucaparib and PLX038

Dose level	Rucaparib dose modifications (mg BID)		
	100%	First dose reduction	Second dose reduction
1B	300	200	NA (participant will be taken off rucaparib treatment)
2B	300	200	NA (participant will be taken off rucaparib treatment)
3B	300	200	NA (participant will be taken off rucaparib treatment)

Dose level	PLX038 dose modifications (mg/m^2)		
	100%	First dose reduction	Second dose reduction
1B	580	300	NA (participant will be taken off PLX038 treatment)
2B	870	580	300
3B	1000	870	580

3.4.2.1 PLX038 toxicity management

Grades 1 and 2 do not need dose adjustments

For grades 3 and 4, dose should be interrupted for up to 21 days. If resolved to Grade 2 or less, reduced Dose (see **Table 10**) will be used during next treatment cycle. If not resolved during 21 days, participant will be taken off PLX038 treatment. Note: grade 3 nausea which resolves to grade 1 within 7 days with appropriate supportive care and grade 3/4 lymphopenia do not need dose adjustments.

3.4.2.2 Rucaparib toxicity management

Grades 1 and 2 do not need dose adjustments

For grades 3 and 4, dose should be interrupted for up to 21 days. If resolved to Grade 2 or less, reduced Dose (see **Table 10**) will be used during next treatment cycle. If not resolved during 21

days, participant will be taken off PLX038 treatment. Note: grade 3 nausea which resolves to grade 1 within 7 days with appropriate supportive care and grade 3/4 lymphopenia do not need dose adjustments.

3.5 Study Calendar

Procedure	Screening[1]	Baseline/ C1D1[1]	C1					All Subsequent Cycles Day 1 [1] (Cycle=21+7 days[2])	30 Days Safety FU[11,13]	Long Term FU[12]
			C1D4	C1D6	C1D7	C1D8	C1D10			
PLX038[2]		X						X		
Rucaparib[3]				X →				X		
Medical History	X									
Height	X									
Histologic confirmation of disease	X									
UGT1A1 testing	X									
EKG	X									
Physical exam, weight and ECOG	X							X	X	
Vital Signs	X							X[4]	X	
CBC w/differential, platelets	X						X[14]	X	X	
Cholesterol	X							X[16]		
PT/PTT	X									
Biochemical profile[5]	X							X	X	
Radiologic Evaluation	X	X						X[6]		X
Brain MRI if clinically indicated	X									

Procedure	Screening[1]	Baseline/ C1D1[1]	C1					All Subsequent Cycles Day 1 [1] (Cycle=21+7 days[2])	30 Days Safety FU[11,13]	Long Term FU[12]
			C1D4	C1D6	C1D7	C1D8	C1D10			
Tumor evaluation / tumor measurements[6]	X	X						X		X
Urinalysis	X									
Serum or urine pregnancy test	X[1]							X		
Concomitant medications		X						X		
Adverse event evaluation								X	X	
Baseline symptoms evaluation		X								
Tumor biopsy[7]		X	X (day 4 or day 6)		X (between day 7-14)					
Research blood for PLX038 level[8]		X		X				X		
Research blood for rucaparib level[9]						X		X		
Research blood for Immune Subset Analysis[17]		X			X			X		
Research blood for germline DNA		X								
Research blood for PBMC PARylation and gH2AX[18]		X		X	X			X		
Research blood for Circulating tumor DNA[19]		X						X		

Procedure	Screening[1]	Baseline/ C1D1[1]	C1					All Subsequent Cycles Day 1 [1] (Cycle=21+7 days[2])	30 Days Safety FU[11,13]	Long Term FU[12]
			C1D4	C1D6	C1D7	C1D8	C1D10			
Research blood for PLX038 coagulation studies[20]		X						X		
Collection of archival tumor samples for research[15]		X								
Collection of hair follicles[10]		X		X	X			X		
Phone call or e-mail for survival every 6 month										X

1. Baseline and C1D1 evaluations do not need to be repeated if performed at screening or baseline in designated time frame. All evaluations will be done within 14 days before treatment initiation on Day 1 of Cycle 1(except for pregnancy test which should be performed within 7 days). If treatment does not start within 28 days after enrollment, screening evaluations will be repeated. For all subsequent cycles, all evaluations are to be done within 7 days of cycle treatment initiation.
2. PLX038 via IV infusion on Day 1 of each cycle. Note: A cycle may vary in length (21 (+ 7) days) due to logistical reasons. PLX038 will be administered as a 1 hour (-10 minutes / +30 minutes) IV infusion.
3. PO, BID on days 6-19 of every 21 days cycle. If cycle length varies, note that approximately 5 days must elapse between last dose of PLX038 and rucaparib.
4. Vital signs will be collected within 1 hour before PLX038 infusions, at least once during the infusions, and within 30 minutes after the completion of the infusion.
5. Biochemical Profile: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid.
6. CT/MRI of chest, abdomen and pelvis at screening/baseline and every 9 (+/-1) weeks after start of study therapy. If participant is taken off treatment for reason other than disease progression, imaging will continue during follow-up until disease progression.
7. Optional tumor biopsies may be performed at baseline, on day 4 or 6 of Cycle 1 (prior to rucaparib dosing) and between days 7 and 14 of Cycle 1.
8. Cycle 1 day 1: before PLX038 infusion, end of infusion (EOI) (+5 minutes), 2 (+/- 15 minutes) hours, 4 (+/- 15 minutes) hours and 24 (+/- 30 minutes) hours post EOI; cycle 1 day 6: just before starting rucaparib, cycle 2 day 1: before PLX038 infusion.
9. Cycle 1 day 8 (optional): before rucaparib, 2 hours (+/- 15 minutes), 3 hours (+/- 15 minutes), 4 hours (+/- 15 minutes) and 24 hours (+/- 1 hour) post rucaparib dosing. Samples will also be collected on day 1 of all subsequent cycles before PLX038 dosing.

10. Collected pre-treatments on C1D1, C1D6 and C1D7 (24 hours after rucaparib dosing) and C2D1 before PLX038 infusion. To minimize participant discomfort, if good quality hair follicles are not collected at baseline (C1D1) or at the second collection (C1D6), no further hair collection will be done.
11. Follow up visit is planned to be performed at 30 (+/- 7 days) after treatment discontinuation to evaluate participant's safety.
12. After safety FU visit, subjects will be followed every 6 months (± 1 month) for survival by phone call or e-mail. **NOTE:** if participant is taken off treatment for reason other than disease progression, we will continue to invite participant every 9 (+/-1) weeks for imaging studies. Outside scans are acceptable.
13. If subjects are not willing to come to NIH for FU visits, they will be contacted by phone call or e-mail for adverse events (refer to **6.1** for AE collection).
14. Sample will be collected on C1D10 +/- 3 days.
15. Collection of available unstained slides or a block from previous biopsies/surgeries for research will be done within 14 days per **2.4**.
16. Cholesterol will be monitored at least once at the C3D1 or C4D1 timepoint or earlier in the treatment regimen.
17. Immune Subset Analysis research blood will be collected at PLX038 Pre-treatment on C1D1, C1D7 (24 hours after rucaparib) and PLX038 pre-treatment C2D1 per **5.3.5**.
18. PBMC PARylation and gH2AX research blood will be collected at C1D1 (before PLX038), C1D6 (prior to rucaparib), C1D7 (24 hours after rucaparib), C2D1 (before PLX038). Blood sample does not need to be collected if hair sample is not collected.
19. Circulating tumor DNA research blood will be collected at PLX038 pre-treatment on C1D1, C2D1 and at disease progression.
20. PLX038 coagulation assay blood will be collection C1D1 before PLX038, C1D1 2 hours post PLX038 EOI and C2D1 before PLX038.

3.6 Cost and Compensation

3.6.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.6.2 Compensation

N/A

3.6.3 Reimbursement

This study offers subject reimbursement or payment for travel, lodging and/or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of the expenses. Some of the costs may be paid directly by the NIH and some may be reimbursed to the subject. Someone will work with subjects to provide more information.

3.7 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, efforts must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.7.1 Criteria for Removal from Protocol Therapy

- Progressive disease
- Excessive toxicity attributed to both drugs (see sections **3.1.2** and **3.4**)
- PI discretion
- Positive pregnancy test
- PLX038 and rucaparib become unavailable

3.7.2 Off -Study Criteria

- Death
- Participant request to be withdrawn from study
- PI discretion
- Lost to follow up
- PI decision to end the study

3.7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visits and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (telephone calls and if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

All routine and appropriate supportive care (including blood products) will be provided during this study, as clinically indicated, and in accordance with the standard of care practices. Clinical judgment should be utilized in the treatment of any AE experienced by the participant.

4.1 Prohibited Medications

4.1.1 Strong inducers or inhibitors of CYP3A4 and UGT1A1 inhibitors

Strong inducers or inhibitors of CYP3A4 and drugs that inhibit UGT1A1 should not be administered while on study treatment. UGT1A1 inhibitors include indinavir, atazanavir, nilotinib, and sorafenib (as well as certain herbal extracts). Additional guidance can be found in the following link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.

4.2 Required Medication

4.2.1 G-CSF

Granulocyte-colony stimulating factors (G-CSF) are required to be administered prophylactically for all participants to prevent/treat neutropenia. G-CSF will be administered at least 72-hours after the dose of PLX038 in each cycle, with at least 14 days elapsing until the next planned chemotherapy dose..

4.3 Recommended Medication

Participants will be recommended to take 8 mg of ondansetron with a small meal or snack to prevent nausea and vomiting approximately 30 minutes prior to each dose of rucaparib.

5 CORRELATIVES STUDIES FOR RESERACH

5.1 Biospecimen Collection

A description of correlative studies including a brief statement of rationale and processing information is made below.

Test/assay	Sample volume (approx.)	Type of tube[a]	Collection timepoint	Location of specimen
Peripheral blood				
PLX038 Pharmacokinetic Analysis	5 mL	6 mL Purple (LVV) tube	1) C1D1 o before PLX038 o EOI (+5 minutes) o 2 hours post EOI (+/- 15 min) o 4 hours post EOI (+/- 15 min) o 24 hours post EOI (+/- 30 min) 2) C1D6 (before rucaparib) 3) C2D1 (before PLX038)	Blood Processing Core (BPC)
Rucaparib Pharmacokinetic Analysis	5 mL	6 mL Purple (LVV) tube	1) C1D8 (optional) o before rucaparib o 2 hours post dosing (+/- 15 min) o 3 hours post dosing (+/- 15 min) o 4 hours post dosing (+/- 15 min) o 24 hours post dosing (+/- 60 min) 2) C2D1 (before PLX038) 3) C3D1 (before PLX038) 4) C4D1 (before PLX038)	
Immune subset analysis	16 ml	8ml CPT citrate blue/black top tubes	1) C1D1 (before PLX038) 2) C1D7 (24 hours after rucaparib) 3) C2D1 (before PLX038)	DTB Clinical Translational Unit
Blood for germline DNA	3ml	3ml light blue citrate tube	1) Baseline	Blood Processing Core (BPC)

Test/assay	Sample volume (approx.)	Type of tube[a]	Collection timepoint	Location of specimen
PBMC PARylation and gH2AX[b]	5ml	6 mL Purple (LVV) tube	1) C1D1 (before PLX038) 2) C1D6 (prior to rucaparib) 3) C1D7 (24 hours after rucaparib) 2) C2D1 (before PLX038)	Blood Processing Core (BPC), analysis to be performed by Suresh Kumar, DTB
Circulating tumor DNA	10ml	cfDNA Streck tubes	1) C1D1(before PLX038) 2) C2D1(before PLX038) 4) At progression	Blood Processing Core (BPC)
PLX038 Coagulation Studies	24 mL	3ml light blue citrate tube (8 tubes)	1) C1D1 o before PLX038 o 2 hours post EOI (+/- 15 min) 2) C2D1 (before PLX038)	NIH DLM / Mayo Clinic
Tumor Biopsies				
γH2AX or other DNA damage markers by confocal microscopy/ELISA	Tumor sample		1) C1D1 2) C1D4 or C1D6 (prior to rucaparib) 3) between C1D7 and C1D14	Frozen samples- DTB Clinical Translational Unit Formalin samples- Blood Processing Core (BPC), analysis to be performed by Suresh Kumar, DTB
PARylation by poly (ADP-ribose) assay				
SLFN11 by IHC and/or RNA				
Whole exome sequencing/RNAseq- bulk and or scRNA				

Test/assay	Sample volume (approx.)	Type of tube[a]	Collection timepoint	Location of specimen
Archival tumor				
Whole exome sequencing/RNAseq	N/A (Archival tumor)		Baseline	Blood Processing Core (BPC), analysis to be performed by Suresh Kumar, DTB
Hair follicles				
yH2AX by confocal microscope/ELISA	N/A (Hair follicles)		1) C1D1 (before PLX038) 2) C1D6 (prior to rucaparib) 3) C1D7 (24 hours after rucaparib) 4) C2D1 (before PLX038)	Christophe Redon, DTB

a. Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.
b. Blood sample does not need to be collected if hair sample is not collected.

5.2 Collection of Samples

5.2.1 Blood

Blood samples for PK will be collected at time points indicated in the Study Calendar **3.5**. PK blood samples will be sent and processed by the Blood Processing Core (BPC). Non-PK blood samples will be sent to and processed by the DTB Clinical Translational Unit.

5.2.2 Tumor samples

All possible attempts will be made to acquire archival pathologic tissue (i.e. original slides or paraffin blocks) or fresh frozen tumor (where available) for purpose of molecular studies. If a tumor block is not available, at least 20 unstained slides may be collected.

Three optional tumor biopsies may be performed at time points indicated in Study Calendar **3.5**. Frozen tumor samples will be procured by the DTB Clinical Translational Unit. Tissue for formalin fixation will be sent to the Laboratory of Pathology. Formalin-fixed samples will be analyzed for disease first, leftover will be used for research. Germline DNA will be collected for accurate culling of somatic variants from the tumor sample.

5.2.3 Hair follicles

Hair follicles will be collected at time points indicated in the Study Calendar **3.5**. Upon delivery in Dr. Redon lab, hairs will be fixed with paraformaldehyde and analyzed under a dissection microscope to select those containing a full intact follicle and sheath.

5.3 Correlative Studies for Research

5.3.1 Pharmacokinetic analysis

Blood samples for the determination of PLX038 and rucaparib plasma trough levels will be obtained from participating participants at time points indicated in Study Calendar **3.5**. Bioanalytical measurements will be conducted by the Clinical Pharmacology Program (CPP).

Blood samples for the determination of Rucaparib will be collected in room temperature lavender-top (EDTA) tubes.

The PLX038 collection tubes will also be lavender-top, but be pre-chilled and contain 1M citrate buffer with 0.1% Pluronic F68, pH4.5 in a 1:10 ratio with the volume of blood drawn. Tubes can be prechilled by completely immersing blood collection tube in bag of ice. After draw, gently invert the tube 3-5 times and immediately immerse the tube into the ice. Specimen must be processed within 1 hour of draw.

Page Figg lab for sample pick up at 102-11964.

5.3.2 The formation of γH2AX foci

γH2AX, the phosphorylated form of histone H2A histone family member X (H2AX) at serine 139, is a marker of DNA double-strand breaks. The formation of γH2AX foci of will be evaluated on plucked hair follicles and tumor by ELISA/confocal microscope. Plucked hairs and tumor will be fluorescently stained for γ-H2AX.

5.3.3 PARP inhibition

PARP inhibition will be evaluated in pharmacodynamic studies by means of a functional assay (Mesoscale Discovery) involving the analysis of poly(ADP-ribose) (PAR) formation from

peripheral-blood mononuclear cells and tumor-tissue cell lysates, all normalized to the amount of PARP1 protein present.

5.3.4 SLFN11

Expression of the gene SLFN11 has been found to correlate with the activity of topoisomerase inhibitors in studies using the National Cancer Institute cell line panel (NCI60) and the Cancer Cell Line Encyclopedia (CCLE) [44, 45]. SLFN11 expression predicted sensitivity to DNA damaging chemotherapy including Top1 and Top2 inhibitors, alkylating agents, platinum derivatives, DNA synthesis and PARP inhibitors [44-46]. In experiments using cells with endogenously high and low SLFN11 expression and siRNA- and Crispr-mediated silencing, SLFN11 was found to be causative in determining cell cycle arrest and cell death in response to DNA damaging agents in cancer cells [46]. Data from the CCLE, the NCI60 and The Cancer Genome Atlas (TCGA) indicate a broad range of SLFN11 expression in lung cancers, raising the possibility that high SLFN11 expression might enrich for tumors that are more likely to respond to DNA damaging chemotherapy; conversely low SLFN11 expression may predict tumors that are likely resistant.

SLFN11 is frequently inactivated in cancer cell lines and has been shown to sensitize cancer cells to anticancer drugs. In particular, elevated SLFN11 expression is associated with sensitivity to DNA-damaging agents which concurrently promote replication fork stalling and cell cycle checkpoint activation, and induce replication stress [47].

SLFN11 is highly expressed in SCLC as compared with other histologies [23]. In contrast, SLFN11 expression is low to nearly absent in lung squamous cell carcinoma and adenocarcinoma [48]. SLFN11 expression has a bimodal distribution in SCLC and may provide meaningful stratification as a predictive biomarker in clinical studies of SCLC. SLFN11 gene expression by RNA-Seq is concordant with SLFN11 protein expression by quantitative western blot.

SCLC cells with high SLFN11 expression are more sensitive to DNA-damaging chemotherapy, and SLFN11 inactivation confers resistance to these agents [23]. Participants with SLFN11-positive tumors treated with a combination of temozolomide and veliparib had a significantly prolonged PFS and OS compared with participants with SLFN11-negative tumors. Consistent with its role in determining chemosensitivity, SLFN11 expression is higher in tumors from SCLC participants who respond to DNA-damaging therapy versus those who do not and is higher in tumors from treatment-naive SCLC participants than in recurrent/relapsed SCLC [48]. Recent studies have shown that SLFN11 suppression by epigenetic silencing could be causal to acquired resistance to DNA-damaging chemotherapy in SCLC [48-50].

Based on the above considerations, we hypothesize that relapsed SCLC tumors with high SLFN11 expression would be sensitive to PARP inhibitors and camptothecins.

Pre-treatment SLFN11 expression in tumor samples will be assessed (IHC and RNA sequence (Section **5.3.8**)) to assess in an exploratory manner, the potentially role of SLFN11 as a predictor of response to PLX038 plus rucaparib.

5.3.5 Immune Subset Analysis

Peripheral blood will be drawn into two 8ml BD Vacutainer Cell Preparation Tubes (CPT) with Sodium Citrate per **3.5** and **5.2**.

Depending on viable PBMC number, the following immune subsets will be assessed using multiparameter flow cytometry including but not necessarily limited to CD8+ T-cells, CD4+Foxp3- T-cells, Tregs, monocyte subsets, MDSC subsets. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4, PD-L1, HLA-DR and/or CD40.

5.3.6 Circulating Tumor DNA

Circulating tumor DNA is a promising biomarker that is being investigated in multiple tumor types. Changes in the levels of circulating tumor DNA can be used to monitor disease course, treatment responses, and recurrences.

5.3.7 Interference of PLX038 with coagulation assays

On 20C0013 to date, after PLX038 infusion, 100% of patient who had post-infusions PTT checked, had new prolonged PTTs. Extensive evaluation in one patient showed that that the PTT prolongation was assay-specific and therefore did not representative of a true coagulation defect. Specifically, there was prolongation of the PTT using an assay with rabbit cephalin phospholipid with micronized silica activator but not with other PTT assays, suggesting *in vitro* assay interference but not a true *in vivo* coagulation defect such as an acquired clotting factor inhibitor. This has great significance for acutely ill patients with cancer receiving this drug, since interventions to treat an *in vivo* "inhibitor" that is a laboratory artifact would result in extended hospitalizations and unwarranted treatments with potentially toxic agents. A similar pattern has been described of a few other pegylated agents [51-54].

We hypothesize that PLX038 will interfere with PTT assays that use the micronized silica or colloidal silica dispersion activators, but not with other PTT assays, including those using kaolin, polyphenolic, or colloidal silica activators, based on the pattern described for a small few other pegylated agents and the mechanism of coagulation activation in these various assays [51-54]. We hypothesize that the remainder of the coagulation assays will be unaffected. We also hypothesize that the degree of interference will relate to the time of sampling post-dose administration, with the *in vivo* trough drug level showing less impact

Pre- and post-PLX038 infusion samples will be drawn to perform coagulation assays, including PT, PTT, thrombin time, reptilase time, fibrinogen, and lupus anticoagulant, using two different instrument analyzers and various reagents. *In vitro* studies using normal donor plasma will further investigate the interference. Normal donor samples will be spiked with varying concentrations of PLX038, PEG alone and SN-38. The resulting samples will be analyzed with coagulation assays shown in **Table 11**.

Testing will be completed at NIH Department of Laboratory Medicine and Mayo Clinic Laboratories.

Table 11. Coagulation Assays

Test	Instrument	Assay	Location of testing
PT/INR	**Stago**	STA Neoplastine CI Plus 10	NIH
	IL	RecombiPlasTin 2g	MAYO
PTT	**Stago**	STA-PTT Automate 5	NIH

Test	Instrument	Assay	Location of testing
		STA-C.K. Prest 5	NIH
		STA-Cephascreen 4	NIH
		STA-Cephascreen 10	NIH
		STA-STACLOT dRVV Screen 2	NIH
		STA-STACLOT dRVV Screen 5	NIH
		STA-STACLOT dRVV Confirm	NIH
		PTT-LA Screen	NIH
		Staclot LA	NIH
		Precision BioLogic CRYO*check* LA/LA sure	NIH
	IL	HemosIL Synth ASil	MAYO
		HemosIL SynthAFax	MAYO
		HemosIL APTT-SP	MAYO
Thrombin Time	**Stago**	STA Thrombin 2	NIH
	IL	HemosIL Thrombin Time	MAYO
Reptilase time	**Stago**	STA-Reptilase	NIH
	IL	Reptilase time	MAYO
Fibrinogen	**Stago**	STA Fibrinogen 5	NIH
	IL	Fibrinogen C	MAYO
		Q.F.A. Thrombin	MAYO

Stago = Diagnostica Stago STA-R Evolution Analyzer. IL = Instrumentation Laboratory ACL Top 700Samples for Genetic/Genomic Analysis

5.3.8 SLFN11 Expression

SLFN11 expression will be assessed by RNA sequencing and or IHC.

5.3.9 RNAseq and Whole Exome Sequencing

In order to address the exploratory goal of characterizing predictive biomarkers of response, genomic analysis including but not limited to RNAseq and whole exome sequencing of tumor tissue may be performed.

5.3.10 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists. Subjects will be contacted at that time with a request to provide a sample to be sent to a CLIA certified laboratory.

5.3.11 Genetic Counseling

If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling with the NCI Genetics Branch to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense). This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

5.4 Sample Storage, Tracking And Disposition

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.4.1 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

BPC contact information

Please e-mail at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.4.1.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) (Dr. Figg's lab) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants without Labmatrix access. The data recorded for each sample may include the participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.4.1.2 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80^{0}C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the NIH Intramural IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with NIH Intramural IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following NIH Intramural IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested). The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

5.4.2 Procedures for storage of participant samples in the DTB Clinical Translational Unit

Contact the DTB Clinical Translational Unit by email (Sunmin Lee: leesun@mail.nih.gov) when the participant is scheduled and by phone as soon as the blood is drawn at 240-760-6330. A lab member will come to pick up the blood. Please keep blood at ambient temperature. Members of the lab will enter the samples into a secure password protected participant's sample tracking database (Translational Pharmacodynamics Research Group Patient Sample Management System) and process the samples.

Sample barcodes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol. It is critical that the sample remains coded and linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate with these variables.

Blood samples will be stored initially in the DTB Clinical Translational Unit in the Magnuson Clinical Center. If, at any time, a subject withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested).

When a participant withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

5.4.3 Procedures for storage of participant samples in the Laboratory of Dr. Redon

Participant samples, collected for the purpose of research under NIH Intramural IRB approved protocols, may be archived in the Dr. Redon laboratory. All data associated with archived clinical research samples is entered into the web-based NCI Labmatrix database, centralized system with access controlled via centralized login. Access to this database is limited to Dr Redon research staff, requiring individual login and password.

The data recorded for each sample may include the participant ID, trial name/protocol number, date drawn/collected, treatment cycle/post-transplant time point, cell source (e.g. peripheral blood, marrow, tissue) as well as box and freezer location. All received samples will receive a unique bar code number, which will be added to the sample NCI Labmatrix database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to participants without authorized access to the NCI Labmatrix database.

Samples are stored in freezers at -80^{0}C (sera, plasma, tissue samples) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at the Dr. Redon laboratory. Access to samples from a protocol for research purposes will be by permission of the Principal Investigator

At least 24 hours prior to the start of the study, the research nurse will contact Dr. Redon in Dr. Aladjem's lab (DTB-LMP/CCR/NCI, Bldg. 37/ Rm 5056) to inform him when samples will be taken (Tel: 240-760-7338 (L); 301-760-6275 (Cell); redonc@mail.nih.gov). Dr. Redon will provide tubes for collecting the plucked hairs. The tubes contain ice cold PBS labeled with the date/time of sampling, the protocol, and the unique identifier. Dr. Redon should be notified of when the samples should be picked up.

5.4.4 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not embedded in paraffin is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the participant was enrolled.

5.4.5 Procedures for storage of tissue and blood samples in the Laboratory of Dr. Kumar

5.4.5.1 Blood Samples

The samples must be stored under conditions in which the analytes are known to be in stable conditions. The blood samples should be refrigerated during the short period, immediately after the centrifugation for plasma and serum, will be barcoded and stored in -80° freezer (Thermofisher TSX series) located in building 37, room 5056. Sample barcodes are linked to participant demographics and limited clinical information. The -80° freezer should be locked all the time, and the key should be in the safe custody of the lab manager. The samples should be entered in the LabMatrix software. PI and research personal can access LabMatrix and locate the samples at any time for future use. The samples should be logged in the research laboratory. Concerned research personnel can access the samples, and the samples should be returned to the same location if leftover research materials is available. The samples should be maintained under appropriate conditions until disposal is authorized. Disposal of the sample should also be recorded in the LabMatrix in the system.

5.4.5.2 Tissue Samples

The biopsy sample will be collected in a liquid nitrogen canister and transferred to the research laboratory. The barcoded samples should be stored in -80° freezer and entered in the Labmatrix software. The -80° Freezer should be locked all the time, and the key should be in the safe custody of the lab manager. The samples should be entered in the LabMatrix software. Sample barcodes are linked to participant demographics and limited clinical information. PI and research personnel can access LabMatrix and locate the samples at any time for future use. The samples should be

logged in the research laboratory. Concerned research personal can access the samples, and the samples should be returned to the same location if leftover research materials is available. The samples should be maintained under appropriate conditions until disposal is authorized. Disposal of the sample should also be recorded in the LabMatrix in the system.

Samples will be disposed of after the final report is issued or when required by directives given in the informed consent paperwork for clinical studies. The research laboratory should document that the samples have been disposed of (LabMatrix) at the time of disposal. For the sample disposal, we will follow the NIH regulations.

5.4.6 Procedures for Storage of PLX038 Coagulation Assay Blood Samples in the Department of Laboratory Medicine (DLM)

The DLM provides laboratory testing for all Clinical Center inpatients and clinic outpatients. The hospital-wide information system (CRIS) is used for ordering a request analyte. The laboratory information system (LIS) is used for reporting laboratory tests and is interfaced with CRIS. Test results are available in CRIS as soon as they are verified in the LIS.

Tests that are run by DLM will be performed on a fresh sample or on batched frozen samples. During this time, the plasma will be separated and stored at -80° C in a DLM freezer. Frozen samples will be batched and sent to Mayo Clinic periodically. DLM uses patient labels generated from LIS system with patient identification such as MRN, LIS # and patient full name on each aliquot sample when stored at -80° C.

5.4.7 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in sections above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the participant withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

6 DATA COLLECTION AND EVALUATION

6.1 Data Collection

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1 of Cycle 1 through 30 days after study agent (s) administration. Beyond 30 days after the last study treatment administration, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE only if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 Data Sharing Plans

6.2.1 Human Data Sharing Plan

At the time of publication or shortly thereafter, the PI will share coded linked human data generated in this research for future research

- in a NIH-funded or approved public repository: clinicaltrials.gov and dbGaP
- in BTRIS
- in publication and/or public presentations
- with approved outside collaborators under appropriate agreements

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 Response Criteria

For the purposes of this study, participants should be re-evaluated for response every 9 weeks (+/- 1 week).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [55, 56]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: >20 mm;
- By CT scan:
  - Scan slice thickness 5 mm or under as >10 mm with CT scan
  - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: >10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic 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 participant, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. 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. 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 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.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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 is preferred to evaluation by 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 (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound during 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, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

6.3.3 Response Criteria

6.3.3.1 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 the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.3.2 Evaluation of Non-Target Lesions

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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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 the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated

Non-Target Lesions	New Lesions	Overall Response
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.3.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.4 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP Office of Compliance and Training / IRB Reporting

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Safety Monitoring Committee (SMC)

This protocol will be periodically reviewed by an intramural Safety Monitoring Committee. comprising physicians, biostatisticians and a lay member selected based on experience, area of expertise, reputation for objectivity, absence of conflicts of interest and knowledge of or experience with clinical trial research. Each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC based on the risks presented in the study. Protocols will not be reviewed if there is no accrual within the review period.

The SMC will operate under the rules of an approved charter that will be written and reviewed at the organization meeting of the SMC. Each review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for participant convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the participant or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

8.1.6.1 Rucaparib

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs), as these events have been observed in participants exposed to cytotoxic chemotherapy (e.g., platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib.

Per the Rucaparib Development Safety Update Report 9 issued on 08/11/2020 and IB version 08/23/2020, pneumonitis has been designated as an AESI. Investigators should implement immediately the reporting of any AE of pneumonitis, or any of the following AEs, irrespective of causality assessment and severity, as an AESI (both serious and non-serious) within 24 hours:

- Pneumonitis
- Interstitial lung disease
- Pulmonary fibrosis
- Acute interstitial pneumonitis
- Alveolitis necrotizing
- Alveolitis
- Hypersensitivity pneumonitis
- Organizing pneumonia

The following AESIs are being added per Rucaparib DSUR version 11, dated 8/12/2022:

- Teratogenicity
- New primary malignancies
- QTc interval prolongation

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4.**

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of Expedited Reporting to CCR

As death/hospitalization due to disease progression is part of the study objectives (CBR, OS and PFS) during Phase II and captured as endpoints in this study, death/hospitalization due to disease progression will not be reported in expedited manner to the sponsor during Phase II. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

The Sponsor might request case summaries for those events if, upon review, the Sponsor determines that an aggregate safety report is required (21CFR312.32(c)(1)(iv)).

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreements.

8.6 Reporting Pregnancy

All required pregnancy reports/follow-up to OSRO will be submitted to:
OSROSafety@mail.nih.gov and to the CCR PI and study coordinator.

Forms and instructions can be found here:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 6 months after the last dose of study drug(s).

Pregnancy of the participant's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 6 months after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 Regulatory Reporting for Studies Conducted Under CCR-Sponsored IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 Sponsor Protocol Deviation Reporting

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 Study Objective

10.1.1 Primary Objectives

- Phase I: To identify the maximum tolerated dose (MTD) of PLX038 in combination with rucaparib.
- Phase II: To assess the efficacy with respect to clinical benefit rate (CBR) (CR+PR+SD) for 4 months according to Response Evaluation Criteria (RECIST 1.1) of a combination of PLX038

and rucaparib in previously treated participants with small cell lung cancer and extra-pulmonary small cell carcinomas.

10.1.2 Secondary Objectives

- To assess safety and tolerability of combined treatment of PLX038 and rucaparib
- To determine the progression-free survival
- To determine overall survival
- To assess the clinical response rate (CRR) (CR+PR) according to Response Evaluation Criteria (RECIST 1.1).

10.2 Sample Size Determination

The initial portion of the trial will be a phase I dose escalation study using a standard 3 + 3 design to determine the MTD over increasing dose levels of rucaparib. Prior to amendment version 03/19/2021, 8 patients were treated in phase I using the former dose escalation scheme. Beginning with amendment version 03/19/2021, with up to 3 new dose levels to be explored, no more than 8+18=26 evaluable participants will be treated in phase I.

The phase II portion of the trial will be conducted using a Simon two-stage Minimax design to rule out an unacceptably low 10% clinical benefit rate (CBR: CR+PR+SD for 4 months) (p0=0.10) in favor of a targeted CBR of 30% (p1=0.30). Based on historical controls, observing a CBR of 20% would be considered clinically meaningful in this setting [24]. With alpha=0.10 and beta=0.10, the study will initially enroll 16 evaluable subjects. If 0-1 subjects have clinical benefit, then no more subjects will be enrolled in this cohort. If 2 or more of the first 16 subjects have clinical benefit, then accrual would continue to a total of 25 subjects. If there were 2-4 subjects with clinical benefit in 25 subjects, this would not be considered promising in this population. If there were 5 or more subjects of the 25 (20.0%) who have clinical benefit, this would be sufficiently interesting to warrant further study of this combination in a future randomized trial comparing this combination with the standard of care. The probability of early termination is 51.5% if the true response rate were 10%.

In addition, up to 10 participants with extrapulmonary small cell cancers may be enrolled on the protocol. The CBR of these participants will not be included in the primary statistical analysis and will be described in an exploratory manner.

The theoretical maximum number of subjects required to determine the MTD in the phase I portion of the study is 26 subjects (8 from before amendment version 03/19/2021 and 6 per dose level for 3 dose levels, although as few as 8+12=20 subjects in 3 dose levels could ascertain the MTD including the participants previously treated before amendment version 03/19/2021). For the phase II portion of the study, 25 evaluable subjects with SCLC and 10 subjects with extrapulmonary small cell cancers are to be recruited. Depending on the number of subjects needed to determine the MTD, and if any of the participants enrolled on the MTD level during phase I have SCLC are eligible for inclusion among those on the phase II portion, planned enrollment is expected to be no more than 26+25+10=61 participants. To allow for the possibility of a small number of inevaluable participants, the accrual ceiling will be set at 65. If the study can accrue 12-15 participants per year, accrual is expected to be completed in 4-5 years.

10.3 Populations for Analyses

All participants who received at least one dose of both treatments and had at least one post-baseline tumor assessment will be evaluated for response. In addition, any treated participants who exhibited clinical progression before being evaluated for clinical response will be included in the analysis.

Participant will be eligible for the DLT evaluation if at least ≥85 percent of rucaparib scheduled doses were taken within the DLT period.

10.4 Statistical Analyses

10.4.1 General Approach

The fraction of participants who experience a clinical benefit (CR+PR+SD longer than 4 months) will be reported along with confidence intervals.

10.4.2 Analysis of the Primary Efficacy Endpoints

The fraction of evaluable participants who experience clinical benefit will be determined along with a two-sided 95% confidence interval.

10.4.3 Analysis of the Secondary Efficacy Endpoints

The safety of the treatment will be monitored, and any toxicities identified will be reported by type and grade.

Among participants in the phase IIA cohort, overall survival (OS) and progression free survival (PFS) will be calculated from the on-study date using the Kaplan-Meier method, along with 95% confidence intervals on the median OS and PFS.

The fraction of participants who experience a clinical response (CR+PR) will be reported along with a 95% confidence interval.

10.4.4 Safety Analyses

Participants will be assessed for toxicity by reporting the grades of toxicity and the type of toxicity observed for all participants, focusing on participants during the phase I evaluation.

MTD will be determined per section **3.1.2**.

10.4.5 Baseline Descriptive Statistics

Baseline demographic characteristics will be reported.

10.4.6 Planned Interim Analyses

In the main phase II cohort, an interim evaluation for efficacy will be performed as described in section **10.2**.

10.4.7 Exploratory Analyses

The following objectives will result in descriptive or comparative analyses when adequate data exist to perform them:

- To identify pharmacodynamic markers of response including γ H2AX; comparisons between those with and without clinical benefit may be made using an exact Wilcoxon rank sum test;

- To study HRD markers (using whole exome sequencing and RNAseq) and SLFN11 as predictors of response; comparisons between those with and without clinical benefit may be made using an exact Wilcoxon rank sum test.
- Pharmacokinetics – descriptive analyses only
- Clinical benefit and response rate among participants with extrapulmonary SCLC.
- Immune subset changes, circulating Tumor DNA: descriptive analyses and comparisons between those with and without clinical benefit may be made using an exact Wilcoxon rank sum test.
- Any exploratory evaluations which generate quantitative measures will be done using descriptive statistics including confidence intervals when appropriate. Any statistical tests performed for evaluation of exploratory objectives will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.
- To describe the interference of PLX038 with routine coagulation assays

11 COLLABORATIVE AGREEMENT

11.1 Cooperative Research and Development Agreement (CRADA)

The CRADA for this protocol has been executed between NCI, NIH and ProLynx (CRADA #03286).

11.2 Clinical Trial Agreement (CTA)

The CTA for this protocol has been executed between NCI, NIH and Clovis Oncology (CTA #01141-19).

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale for Subject Selection

No individual who meets the criteria for eligibility will be excluded from participation based on their race, ethnicity, gender, or socioeconomic status. Particular attention will be made to acquire a broad and diversified population.

12.2 Participation of Children

Children (younger than 18 years) will not be included in this protocol due to the limited data on study drugs in children and the different biology of childhood malignancy.

12.3 Evaluation of Benefits and Risks/Discomforts

12.3.1 Benefits

The study drugs may help to control the disease. The results may help the investigators learn more about the disease and develop new treatments for participants with this disease.

12.3.2 Risks

12.3.2.1 Study drugs risks

All care will be taken to minimize study treatment side effects, but they can be unpredictable in nature and severity. Participants will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of participants will be recorded in the participant chart.

12.3.2.1.1 PLX038 risks

The primary risk to participants participating in this research study is from the toxicity of study drugs. See section **1.2.2** and investigator brochure for full information.

12.3.2.1.2 Rucaparib risks

Table 12. Safety Profile of Rucaparib

System Organ Class **Preferred Term**[a]	**Rucaparib (N = 1,871)**			
	TEAEs		**Serious TEAEs**	
	All Grades n (%)	**CTCAE ≥ Grade 3 n (%)**	**Life-threatening (CTCAE grade 4) n (%)**	**Fatal n (%)**
Blood and Lymphatic System Disorders				
Anemia/Hemoglobin decreased[b]	853 (45.6)	474 (25.3)	25 (1.3)	0
Febrile neutropenia	19 (1.0)	18 (1.0)	14 (0.7)	0
Leukopenia/White blood cell count decreased[b]	179 (9.6)	42 (2.2)	8 (0.4)	0
Lymphopenia/Lymphocyte count decreased[b]	68 (3.6)	21 (1.1)	4 (0.2)	0
Neutropenia and/or low/decreased ANC[b]	358 (19.1)	183 (9.8)	53 (2.8)	1 (0.1)
Thrombocytopenia and/or low/decreased platelets[b]	466 (24.9)	129 (6.9)	31 (1.7)	1 (0.1)
Gastrointestinal Disorders				
Diarrhoea	528 (28.2)	29 (1.5)	0	0
Dyspepsia	188 (10.0)	5 (0.3)	0	0
Nausea	1225 (65.5)	64 (3.4)	0	0
Stomatitis	135 (7.2)	4 (0.2)	0	0
Vomiting	648 (34.6)	63 (3.4)	0	0
General disorders and Administration Site Conditions				
Asthenia/Fatigue[b]	1205 (64.4)	166 (8.9)	2 (0.1)	0
Immune System Disorders				
Hypersensitivity[b]	53 (2.8)	0	0	0
Investigations				

ALT/AST increased[b]	699 (37.4)	180 (9.6)	2 (0.1)	0
Blood creatinine increased	321 (17.2)	11 (0.6)	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	530 (28.3)	28 (1.5)	0	0
Nervous system disorders				
Dizziness	273 (14.6)	2 (0.1)	0	0
Dysgeusia	421 (22.5)	1 (0.1)	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnoea	297 (15.9)	18 (1.0)	0	0
Skin and subcutaneous tissue disorders				
Photosensitivity reaction	184 (9.8)	3 (0.2)	0	0

Abbreviations: ADR = adverse drug reaction; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.

[a] PTs were based on MedDRA dictionary. If a patient experiences the same PT (System Organ Class) multiple times, then the patient will be counted only once for that PT.

[b] Combined MedDRA preferred terms.

Data cut-off for each study: CO-338-010 final data is 16 May 2019; CO-338-017 is 01 February 2019; CO-338-014 is 31 December 2019; CO-338-052 is 13 September 2019; and CO-338-043 is 30 September 2020; and CO-338-087 (ATHENA-MONO) is 23 March 2022.

Table 13. Serious Adverse Reactions Considered Expected for Safety Reporting Purposes

ADR List	**Rucaparib (N = 1,871)**
System Organ Class Preferred Term[a]	**SARs n (%)**
Blood and Lymphatic System Disorders	
Anemia/Hemoglobin decreased[b]	89 (4.8)
Febrile neutropenia	15 (0.8)
Leukopenia/White blood cell count decreased[b]	3 (0.2)
Neutropenia and/or low/decreased ANC[b]	12 (0.6)
Thrombocytopenia and/or low/decreased platelets[b]	19 (1.0)
Gastrointestinal Disorders	
Diarrhea	3 (0.2)

Nausea	12 (0.6)
Vomiting	14 (0.7)
General Disorders and Administration Site Conditions	
Asthenia/Fatigue[b]	6 (0.3)
Investigations	
ALT/AST increased[b]	3 (0.2)
Blood creatinine increased	7 (0.4)
Respiratory, Thoracic, and Mediastinal Disorders	
Dyspnea	3 (0.2)

Abbreviations: ADR = adverse drug reaction; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients reporting the event; PT = preferred term; SAR = serious adverse reaction.

a PTs were based on MedDRA dictionary.

b Combined MedDRA preferred terms.

There are no expected life-threatening (Grade 4) or fatal (Grade 5) reactions for rucaparib. Data cut-off for each study: CO-338-010 final data is 16 May 2019; CO-338-017 is 01 February 2019; CO-338-014 is 31 December 2019; CO-338-052 is 13 September 2019; CO-338-043 is 30 September 2020; and CO-338-087 (ATHENA-MONO) is 23 March 2022.

12.3.2.2 Risk of Biopsy

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection, visceral injury, hematoma and death) that will be explained fully during informed consent. The biopsies will be performed in interventional radiology.

12.3.2.3 Risks of exposure to Ionizing Radiation

This research has three optional CT guided biopsies collected for research purposes only and five CT scans per year for disease assessment. Subjects in this study may be exposed to 7.9 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 0.8 out of 100 (0.8%) and of getting a fatal cancer is 0.4 out of 100 (0.4%).

12.3.2.4 Risks of CT Scans

In addition to the radiation risks discussed above, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling.

12.3.2.5 Risks of sedation

Biopsies will be done under sedation. Potential side effects of sedation include headache, nausea and drowsiness. These side effects usually go away quickly

12.3.2.6 Research Blood Collection Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting and infection. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

12.3.2.7 Research Hair Follicles Collection Risks

Risks of hair follicles collection include light pain and discomfort.

12.3.2.8 Other Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

12.3.2.9 Non-Physical Risks of Genetic Research

Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Participants will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with participants, family members or health care providers.

Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the participants, family members or health care providers, this risk will be included in the informed consent document.

12.3.3 Assessment of Potential Risks and Benefits

Solid tumors treatment needs improved therapy options. Currently running studies suggest that use of PLX038 in combination with rucaparib may have tremendous anti-tumor efficacy.

A number of clinically appropriate strategies to minimize risks to participants have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. Overall, the potential benefit of the use of PLX038 in combination with rucaparib in subjects with solid tumors outweigh the risks associated with this drug.

The potential benefit to a participant that participates in this study is better control of their tumor growth and disease recurrence which may or may not have a favorable impact on symptoms and/or survival.

Potential adverse reactions attributable to the administration of the study drugs utilized in this trial are discussed in Sections **1.2.2.3** and **1.2.3.4**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity.

12.4 Consent Process and Documentation

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be

given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, associate investigators, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 PLX038 (IND 145310)

14.1.1 Source

ProLynx LLC will supply investigational PLX038. The PLX038 product was manufactured for Delta-Fly Pharma, Inc as DFP-13318.

14.1.2 Acquisition and Accountability

PLX038 will be provided by ProLynx LLC and delivered directly to the NIH Pharmacy. Individual IV bags will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. IV bags will be delivered from NIH Pharmacy to participant unit where drug will be infused to the participant.

14.1.3 Formulation and Preparation

The lyophilized PLX038 (220 mg/vial) can be reconstituted using 11 mL saline or 5% dextrose, then diluted in saline or 5% dextrose IV bags to final volume of 100 mL or 250 mL, respectively. If the volume of the dose to be administered to the participant exceeds 250 mL, PLX038 may be diluted in saline or 5% dextrose IV bags to a final volume of 500 mL.

14.1.4 Stability and Storage

PLX038 lyophilized product should be stored at 2-8° C.

14.1.5 Administration Procedures

See Section **3.3.1**.

14.1.6 Toxicity

See section **1.2.2.2**.

Refer to investigator brochure for detailed toxicity information.

14.2 Rucaparib (IND 145310)

14.2.1 Source

Investigational supplies of rucaparib will be supplied by Clovis Oncology, Inc

14.2.2 Acquisition and Accountability

Rucaparib will be provided by Clovis Oncology, Inc and delivered directly to the NIH Pharmacy. Individual bottles with tablets will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. Participants will pick up bottles at NIH Pharmacy and will return bottles and not-used tablets after completion of every cycle together with Medication Diary to Study Coordinator. After review of leftover tablets and Medication Diary, unused tablets will be returned to pharmacy and disposed by pharmacy personnel.

14.2.3 Formulation and Preparation

The oral formulation of rucaparib contains the camphor sulfonic acid salt of the active agent rucaparib. All dosage strengths are expressed as the weight of free base rucaparib.

14.2.4 How Supplied

Rucaparib is currently available as 200 mg, 250 mg, and 300 mg immediate-release tablets for oral administration. All tablets are provided in 60ct high-density polyethylene (HDPE) bottles with child-resistant caps. Tablets should be stored as directed on the product label.

14.2.5 Administration

Please see section **3.3.2**.

14.2.6 Toxicity

See section **1.2.3.4**.

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16 APPENDICES

16.1 Appendix A - Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

16.2 Appendix B - Patient's Medication Diary

Cycle_____ Participant's ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment
2. You will take rucaparib twice a day for 14 days on and 7 days off during 21-day cycle
3. Rucaparib should be taken every 12 hours at approximately the same times each day. Doses should be taken within 2 hours of the scheduled time.
4. In case of a missed dose (more than 2 hours late) or vomiting after taking rucaparib, do not make up the missed dose.
5. Record the date, the number of tablets that you took, and when you took them.
6. You may take 8 mg of ondansetron with small meal or snack to prevent nausea and vomiting approximately 30 minutes prior to each dose of rucaparib**.**
7. If you have any comments or notice any side effects, please record them in the comments column.
8. Please bring this form and your bottles (even it is empty) when you come for your clinic visits.

Day	**Date**	**# of Oral Rucaparib Tablets taken (every 12 hours)**		**Comments (side effects or missed doses)**
		AM	**PM**	
1				Do not take rucaparib.
2				Do not take rucaparib.
3				Do not take rucaparib.
4				Do not take rucaparib.
5				Do not take rucaparib.
6				
7				
8				
9				
10				
11				
12				

Day	Date	# of Oral Rucaparib Tablets taken (every 12 hours)		Comments (side effects or missed doses)
		AM	PM	
13				
14				
15				
16				
17				
18				
19				
20	[redacted]	[redacted]	[redacted]	Do not take rucaparib.
21				Do not take rucaparib.

Participant's signature: _____