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S1900A: LOH high and/or deleterious BRCA1/2 mutation - Rucaparib

SWOG

LUNGMAP, A MASTER PROTOCOL TO EVALUATE BIOMARKER-DRIVEN THERAPIES AND IMMUNOTHERAPIES IN PREVIOUSLY-TREATED NON-SMALL CELL LUNG CANCER (Lung-MAP SCREENING STUDY)

S1900A, A PHASE II STUDY OF RUCAPARIB IN PATIENTS WITH GENOMIC LOH HIGH AND/OR DELETERIOUS BRCA1/2 MUTATION STAGE IV OR RECURRENT NON-SMALL CELL LUNG CANCER (Lung-MAP SUB-STUDY)

NCT#: 03845296

Clovis Oncology Protocol #: 338-IIT-094

This is a potential FDA Registration Trial. Additional site requirements include:

- **maintenance of a Trial Master File (https://www.swog.org/sites/default/files/docs/2017-10/Guidance%20on%20FDA%20Inspection.pdf)**
- **completion of a protocol specific Delegation of Task Log (DTL) (see Section 13.2)**
- **additional monitoring (see LUNGMAP Appendix 18.2)**

NOTE: Sites must utilize the CIRB as their IRB of record to participate in this study.

LUNGMAP and its sub-studies are being conducted under SWOG IND 143217 and CIRB. The LUNGMAP Study is considered a single study under one IND, consisting of the Screening Protocol and multiple sub-studies. Each sub-study protocol operates independently and has its own version date. For CIRB Continuing Reviews, LUNGMAP and its sub-studies will be processed separately but have the same expiration date as the LUNGMAP screening protocol.

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory > Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG CRA Workbench via the SWOG website (www.swog.org).

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log in with a CTEP-IAM username and password.

For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email:

206/652-2267
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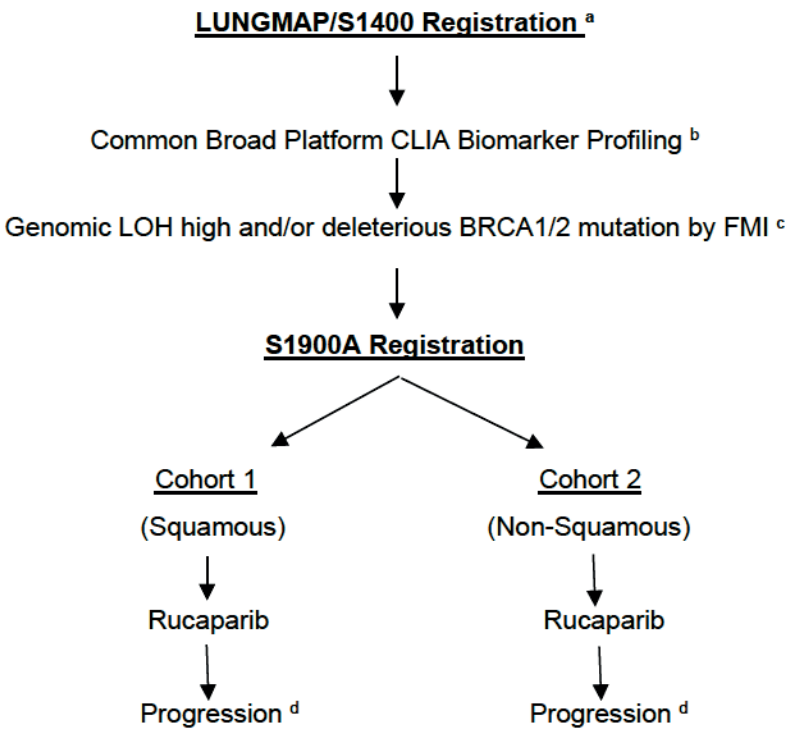
For treatment or toxicity related questions contact S1900AMedicalquery@swog.org.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

SCHEMA



a See **LUNGMAP** Section 5.1 for registration information.
Note: Patients may have been enrolled on the legacy **S1400** screening/pre-screening study.

b Notification of sub-study assignment will be provided by the SWOG Statistics and Data Management Center (SDMC) (see **LUNGMAP** Section 11.0 for details).

c See **S1900A** Section 5.0 for the definition of LOH high and/or deleterious BRCA1/2 mutation by Foundation Medicine Inc. criteria.

d Upon progression (as defined in **S1900A** Section 10.0), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG SDMC (see **S1900A** Section 14.4).

1.0 OBJECTIVES

1.1 Primary Objective

a. To evaluate the overall response rate (ORR) (confirmed and unconfirmed, complete and partial) associated with rucaparib in patients with genomic LOH high and/or deleterious BRCA1/2 mutations within:
   i. Cohort 1: Patients with squamous cell histology
   ii. Cohort 2: Patients with non-squamous histology (adenocarcinoma, large cell, NSCLC NOS, or mixed histology with any non-squamous component)

1.2 Secondary Objectives

a. To evaluate investigator assessed progression-free survival (IA-PFS) and overall survival (OS) associated with rucaparib within each cohort.

b. To evaluate duration of response among responders within each cohort.

c. To evaluate the frequency and severity of toxicities associated with rucaparib among all patients enrolled on the study (combining cohorts).

1.3 Translational Medicine Objectives

a. To evaluate the association between alterations in DNA repair genes and response by RECIST 1.1.

b. To perform comprehensive next-generation sequencing of circulating tumor DNA (ctDNA) at baseline in all patients to assess its clinical utility in comparison to tumor tissue biomarker profiles.

   Note: The proposal to use these specimens would be submitted as an amendment to CTEP for approval prior to SDMC review of assay results.

c. To establish a tissue/blood repository from patients with refractory non-small cell lung cancer (NSCLC).

2.0 BACKGROUND

2.1 Overview

The Lung-MAP study is a master protocol for genomic screening and multi-sub-study testing of drug/biomarker combinations in a Phase II/III setting compatible with subsequent FDA approval. Genomic screening of a large patient resource provided by sites participating in the NCI National Clinical Trials Network (NCTN) identifies a series of molecular targets/biomarkers which are matched to new drugs, leading to appropriate sub-study assignment and drug treatment. Each molecular target in Lung-MAP is represented by a biomarker for which there is an analytically validated diagnostic assay. This approach provides the basis for this large-scale screening/clinical registration trial with the ability to screen patients, either through genomic analysis or immunohistochemistry based assays, with homogeneous eligibility criteria and direct them to a sub-study based on the results of screening diagnostic tests.

Based on the results of the tumor analysis, patients will either be assigned to one of the biomarker-driven sub-studies or to a 'non-match' sub-study for patients with none of the

eligibility biomarkers. The biomarker-driven sub-studies are designed around a genotypically-defined alteration in the tumor and a drug that targets it. The non-match studies are designed around an investigational agent with the potential for efficacy in a broader population. For a full description and justification of the study design, refer to the **LUNGMAP** Screening Protocol.

DNA Damage Repair (DDR) and Synthetic Lethality:
The viability of the cancer cell is highly dependent on effective maintenance of genomic integrity. Since cancer cells are genomically unstable, they are very prone to deleterious changes in critical genes including those that regulate intracellular responses to DNA damage. DDR response involves a set of well-orchestrated intracellular processes that occur in response to endogenous and exogenous insults to the cell genome. *(1)*The specific nature of the DNA damage calls for different DDR mechanisms to affect the needed repair. The base excision repair or single-strand break repair (BER/SSBR), nucleotide excision repair (NER) and mismatch repair (MMR) pathways are responsible for the repair of single strand breaks or replication errors. On the other hand, non-homologous end-joining (NHEJ) and homologous recombination repair (HRR) are responsible for the repair of double strand breaks. The NHEJ results in low-fidelity, error-prone repairs while the HRR pathway is the major mechanism for replication-associated double strand breaks and achieves high fidelity, error-free repair. Defects in DDR genes and or other DNA damage signaling proteins are commonly encountered in sporadic and familial cancers *(2)*. Impaired capacity for DNA damage repair as a result of loss of an important element of a specific DDR pathway can engender a compensatory activity in some of the other proteins involved in the pathway thereby making the cell susceptible to strategies that target this compensating protein. Additionally, there may be an overdependence of the cell on alternative repair pathways distinct from the pathway impaired by the genetic alteration. A classic example of this biological derangement is the impairment of the HRR pathway in patients with BRCA1 or BRCA2 mutation leading to inability of the cell to repair double strand breaks. Such patients are vulnerable to inhibitors of poly (ADP) ribose polymerase (PARP) enzyme because the inactivation of the BER pathway by the PARP inhibitor leads to persistence and progression of single strand breaks to the lethal double strand breaks. The inability of the cells to repair double strand breaks as a consequence of impaired HRR caused by the BRCA mutation results in cell death. This therapeutic construct is aptly referred to as synthetic lethality and was initially demonstrated using BRCA-deficient cell lines leading to clinical evaluation of PARP inhibitors in ovarian and breast cancer harboring deleterious mutations in the BRCA genes. It is now recognized that besides BRCA1 and BRCA2, synthetic lethality can also be induced when genetic mutations affect other critical components of HRR. In addition to these mutations, genomic loss of heterozygosity (LOH) has been shown to be a phenotypic biomarker to identify ovarian cancer patients with impaired DDR. In advanced ovarian cancer, rucaparib demonstrated clinical benefit (increased ORR and prolonged PFS) in LOH high tumors, even if tumors were BRCA wild-type with compared to LOH low ovarian cancers. *(3)* **S1900A** seeks to examine whether BRCA-positive or LOH high NSCLC also derives clinical benefit from rucaparib.

Summary of Biomarker Approach in **S1900A**

On April 6, 2018, the FDA approved rucaparib for the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. In addition to mutations in BRCA1/2, genomic LOH has been shown to be a phenotypic biomarker to identify ovarian cancer patients treated with two or more chemotherapies who are likely to respond to rucaparib.

The FDA also concurrently approved the complementary diagnostic test, FoundationFocusTM CDx BRCA LOH, for tumor samples to determine HRD status.

Patients with deleterious BRCA1/2 mutations and/or LOH high NSCLC detected on the Foundation Medicine assay employed in Lung-MAP will be eligible for this study. In addition to breast and ovarian cancer, PARP inhibitors have demonstrated activity across multiple tumor types harboring deleterious mutations in BRCA1/2 such as: breast, ovarian, prostate and pancreatic adenocarcinoma. *(4,5)*

LOH high tumors are also included as a phenotypic biomarker of HRD. The computational algorithm for genome-wide LOH used in the Foundation One assay for this sub-study is identical to the FDA approved complementary diagnostic test FoundationFocus CDx BRCA LOH for ovarian cancer. For ovarian cancer LOH ≥ 16% is considered high. In this Lung-MAP sub-study for NSCLC a higher cutpoint of ≥ 21% is used to enrich for patients most likely to benefit from PARP inhibition (Figure 1).

Additional genomic aberrations in DNA repair proteins detected on the Foundation Medicine next-generation sequencing assay will be examined on an exploratory basis. Tissue and blood will be banked providing the ability for future exploratory analysis.

Prevalence of BRCA-positive in Lung Cancer:
In squamous histology patients screened on Lung-MAP the prevalence of deleterious BRCA1/2 mutations is 5.8%. Analysis of lung adenocarcinoma patients in The Cancer Genome Atlas (TCGA) indicates 1.4% of patients harbor a deleterious BRCA1/2 mutation.

Prevalence of LOH in Lung Cancer:
The frequency of deleterious alterations (deletions and mutations and copy number variations) in NSCLC has been analyzed in the TCGA. Approximately 25% of cases of squamous lung cancer and 9% of adenocarcinoma had LOH ≥ 21% based on TCGA data. Genomic LOH is a biomarker for DNA-damage that has been shown to confer sensitivity to PARP inhibitors, and can be derived computationally using the existing SNPs on any of Foundation Medicine's tissue-based NGS assays using the ~3500 SNPs on the panel. Examining NSCLC cases from Foundation Medicine, lung adenocarcinoma LOH ≥ 21% was found in approximately 16% in squamous cell lung cancer and likely comparable to TCGA data in lung adenocarcinoma. Based on data examining clinical outcomes of patients with LOH high advanced ovarian cancer treated with rucaparib, we expect LOH high NSCLC will be susceptible to the synthetic lethal effect of rucaparib therapy and will be appropriate for targeted therapy using a PARP inhibitor.

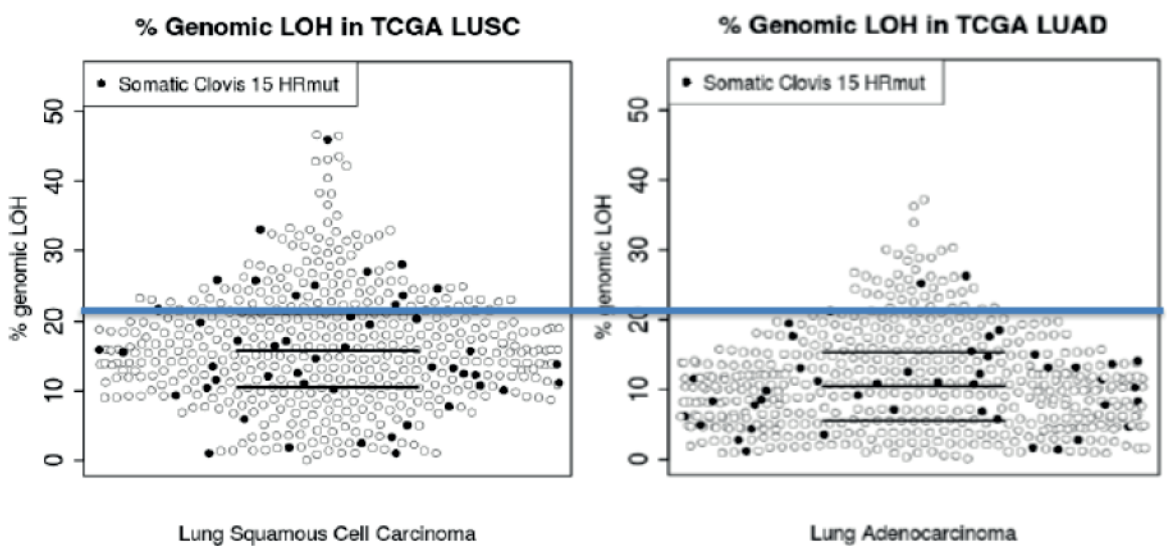


Figure 1: Genomic LOH ≥ 21% in the TCGA by Histology.

Platinum Sensitivity in Lung Cancer:
The objective response to platinum-based frontline chemotherapy and the duration of benefit are strongly correlated. These endpoints are also well-established surrogates for further benefit from salvage therapy and overall patient outcome in ovarian cancer and SCLC. *(6, 7, 8)* Additionally, platinum sensitivity shows significant association with clinical benefit of PARP inhibitors in ovarian cancer and in SCLC patients. *(9, 10)* Retrospective and single institution studies suggested that patients with platinum-sensitive NSCLC achieved better outcome with salvage targeted therapy. *(11)* In squamous lung cancer patients from the TCGA dataset, genomic LOH ≥ 21% was associated with an overall survival (OS) benefit to platinum-based chemotherapy (HR=0.295; p=0.023).

Study Design:
There is limited clinical exploration of single agent PARP inhibitor therapy in lung cancer. The proposed sub-study of rucaparib will be the first prospective study to evaluate the clinical benefit of a PARP inhibitor as a single agent in patients with non-squamous lung cancer in addition to squamous cell lung cancer. It is also the first prospective study in lung cancer to use loss of heterozygosity (LOH) as a selection biomarker. Patients with susceptible tumors defined as LOH ≥ 21% using the ~3500 SNPs on the Foundation Medicine panel will be identified as part of the screening conducted under the Lung-MAP protocol, in addition to those harboring a BRCA1 or BRCA2 mutation. Two cohorts stratified by histology (squamous and non-squamous) will accrue patients with LOH high NSCLC. Rucaparib will be administered orally with each cycle comprising 21 continuous days.

2.2 Rationale

New treatments for advanced NSCLC with progressive disease after chemotherapy, immune checkpoint blockade, or appropriate targeted therapies for oncogene driven subsets of NSCLC remains an acute area of unmet need. The PARP inhibitor rucaparib was granted accelerated approval by the FDA in December 2016 for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) advanced ovarian

cancer. On April 6, 2018, the FDA also approved rucaparib for the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. In addition to mutations in BRCA1/2, genomic LOH has been shown to be a phenotypic biomarker to identify ovarian cancer patients treated with two or more chemotherapies who are likely to respond to rucaparib. *(12)*

The FDA also concurrently approved the complementary diagnostic test, FoundationFocusTM CDx BRCA LOH, for tumor samples to determine HRD status.

This trial seeks to demonstrate whether LOH high and/or deleterious BRCA1/2 mutations, phenotypic biomarkers that has been shown to confer sensitivity to rucaparib in ovarian cancer, also confers sensitivity in NSCLC patients. Exploring rucaparib activity in adenocarcinoma and squamous NSCLC with a genomic LOH ≥ 21% will provide a robust evaluation of rucaparib in patients most likely to respond in both histologies.

In addition, the detection rates of mutations observed in ctDNA isolated from patient plasma at baseline will be evaluated in comparison to mutations observed in tumor tissue. It is expected that mutations identified in plasma will be synonymous with those detected in tissue, with the following exceptions: a subset of patients may have insufficient amounts of ctDNA in circulation for detection, and secondly, a subset of patients may have additional mutations detected in plasma that are associated with metastases and not present in the original tissue biopsy. The overarching goal of the Lung-MAP liquid biopsy program, planned across multiple sub-studies, is to assess whether positive identification of mutations in ctDNA can be utilized for molecular assignment. In this sub-study, the primary objective is to correlate detection frequencies between tissue and plasma.

If the requisite number of objective responses is observed, this is a signal to move forward to larger, randomized later stage trials in both the treatment and maintenance setting following platinum-based chemotherapy. A positive study would support genomic LOH as a biomarker for rucaparib and PARP inhibitor drug development in NSCLC, whereas a negative study would show a lack of benefit of rucaparib in NSCLC.

2.3 Data

Rucaparib has been evaluated in Phase 1 and 2 clinical studies and is being evaluated in ongoing Phase 2 and Phase 3 clinical studies. The oral formulation as monotherapy is the focus of current development efforts.

An overview of data from nonclinical and clinical studies of rucaparib are provided below and described in detail in the rucaparib Investigator's Brochure (IB). A summary of the benefit: risk is also provided in the rucaparib IB.

In Part 1 of the ARIEL2 study, patients with recurrent, platinum-sensitive, high-grade ovarian carcinoma were classified into one of three predefined homologous recombination deficiency subgroups on the basis of tumor mutational analysis: BRCA mutant (deleterious germline or somatic), BRCA wild-type and LOH high, or BRCA wild-type and LOH low. Patients began treatment with oral rucaparib at 600 mg twice per day for continuous 21-day cycles until disease progression or any other reason for discontinuation. The primary endpoint was progression-free survival (PFS). PFS was significantly longer in the BRCA mutant (hazard ratio 0.27, 95% CI 0.16-0.44, $p<0.0001$) and LOH high (0.62, 0.42-0.90, $p=0.011$) subgroups compared with the LOH low subgroup. Additionally, more patients achieved confirmed RECIST responses, achieved confirmed RECIST and CA-125 responses, and had longer response durations in the LOH high subgroup than in the LOH low subgroup. For example, the ORR was 29% (95% CI 20-40) and 10% (95% CI 4-20) in BRCA wild-type LOH high and low subgroups, respectively. *(13)*

In the ARIEL3 trial that randomized patients with ovarian cancer to receive either rucaparib or placebo as maintenance therapy following response to platinum-based chemotherapy, genomic LOH was used to select potentially select BRCA wild-type patients for improved clinical outcomes to rucaparib. In these patients, the PFS was increased in rucaparib patients as compared to placebo for both the LOH high patients (median PFS 9.7 vs. 5.4 months; HR=0.44, P<0.0001) and LOH low patients (median PFS 6.7 vs. 5.4 months; HR 0.58, p=0.005) (Figure 2). In summary, improved clinical outcomes have been observed in LOH high ovarian cancer patients administered rucaparib in both treatment and maintenance settings. *(14)*

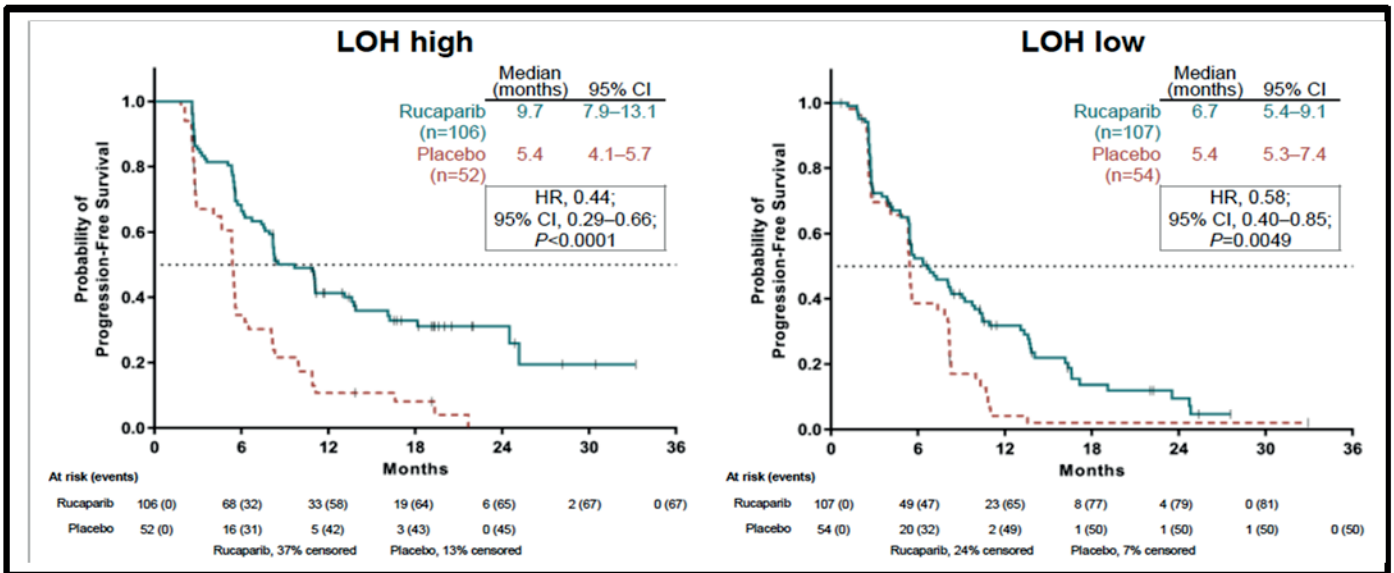


Figure 2: ARIEL 3 Trial: Investigator assessed PFS in BRCA Wild-Type Advanced Ovarian Cancer Patients

A summary of the clinical experience with rucaparib is provided below.

Completed Studies

- A4991002: A Phase 1 open-label, dose-escalation study of IV rucaparib in combination with temozolomide (TMZ) in patients with advanced solid tumors (Part 1) or malignant melanoma (Part 2) *(15)*
- A4991005: A Phase 2, open-label study of IV rucaparib in combination with TMZ in patients with metastatic melanoma. *(16)*
- A4991014: A Phase 1, open-label, dose-escalation study of IV and oral rucaparib administered with different chemotherapeutic agents in patients with an advanced solid tumor. *(17)*
- CO-338-023 (RUCAPANC): A Phase 2, single-arm, open-label study of monotherapy oral rucaparib as treatment for patients with previously treated locally advanced or metastatic pancreatic ductal adenocarcinoma and a known deleterious BRCA mutation.

Ongoing Studies

- CO-338-010: 3-part, open-label, Phase 1/2 study of monotherapy oral rucaparib. (18)
    - Part 1: Phase 1 portion evaluating PK and safety of escalating doses of rucaparib in patients with solid tumors; this portion identified 600 mg twice daily (BID) as the recommended starting dose for future studies (n = 56; completed).
    - Part 2: A Phase 2 portion evaluating the efficacy and safety of rucaparib in patients with relapsed, high-grade ovarian cancer associated with a BRCA mutation.
    - Part 3: A Phase 2 portion in patients with a relapsed solid tumor associated with a BRCA mutation in order to characterize the PK, food effect, and safety profile of a higher dose strength tablet (n = 26; enrollment complete).
- CO-338-017 (ARIEL2): A 2-part open-label Phase 2 study of monotherapy oral rucaparib for treatment of relapsed, high-grade ovarian cancer patients. Patients will be classified into molecularly-defined subgroups, including tumor BRCA (tBRCA, inclusive of both germline and somatic BRCA) and BRCA-like, by a prospectively defined genomic signature. *(19)*
- CO-338-014 (ARIEL3): A Phase 3, randomized, double-blind study of monotherapy oral rucaparib versus placebo as switch maintenance treatment in patients with platinum-sensitive-, relapsed, high-grade ovarian cancer who achieved a response to platinum-based chemotherapy. *(20)*
- CO-338-044 (DDI study): A 2-part, Phase 1, open-label, multiple-probe drug-drug interaction (DDI) study.
- CO-338-043 [ARIEL4] is evaluating rucaparib versus chemotherapy as treatment for patients with relapsed high-grade ovarian cancer associated with a deleterious BRCA1/2 mutation
- CO-338-045 is an open-label Phase 1, single-dose study of the disposition of [14C]-radiolabel rucaparib in patients with advanced solid tumors.
- CO-338-052 [TRITON2] is a Phase 2 study evaluating rucaparib efficacy in mCRPC whose tumors are associated with HRD by enrolling mCRPC patients with mutations in BRCA1/2, ATM, or other HR genes.
- CO-338-063 [TRITON3] is a Phase 3, randomized, 2-arm study evaluating rucaparib vs. physician's choice (abiraterone acetate, enzalutamide or docetaxel) in patients with mCRPC associated with a deleterious BRCA1/2 or ATM mutation.
- CO-338-078 is a Phase 1, open-label, parallel group study to determine the pharmacokinetics, safety, and tolerability of rucaparib in patients with an advanced solid tumor and either moderate hepatic impairment or normal hepatic function.
- CO-338-085 [ATLAS] is a Phase 2, open-label study evaluating rucaparib for the treatment of patients with locally advanced or metastatic urothelial cancer.

Overview of Pharmacokinetics (PK)

Nonclinical studies: Rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier. In vitro data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs after oral dosing.

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent

inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1) and may inhibit P-gp and BCRP in the gut.

Clinical studies: Assessment of rucaparib PK in cancer patients showed an approximate dose-proportional exposure after once daily (QD) or BID dosing, rapid absorption with maximum plasma concentration (C_{max}) achieved within 1.5 to 6 hours, and distribution into tissue. The oral bioavailability was 36% and terminal half-life ($T_{1/2}$) ranged from 9.23 to 33.6 hours. 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 area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24h}) of rucaparib by 20% and 38%, respectively, and delayed the median time to occurrence of C_{max} (T_{max}) by approximately 2.5 hours as compared with these parameters 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.

In a preliminary assessment of rucaparib metabolism in patients, rucaparib biotransformation pathways included hydroxylation or oxidation, N-demethylation, deamination, and phase II methylation. A carboxylic acid metabolite (M324) and a phase II N-methylated metabolite of M324 (M338) were identified as major metabolites.
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 hyperinducers) 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 a 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 patients who are receiving concomitant treatment with a PPI.

Results from Study CO-338-044 evaluating potential drug-drug interactions (DDI) with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on P-gp.

Overview of Efficacy

Efficacy analysis was based on pooled efficacy data from 106 patients with BRCA mutant ovarian cancer, who received two or more prior chemotherapy regimens, and who initiated treatment with rucaparib at 600 mg BID in Part 2A of Study CO-338-010 and Parts 1 and 2 of Study CO-338-017.

Efficacy data indicate that many patients with advanced ovarian cancer associated with a BRCA1/2 gene mutation and who had two or more prior therapies achieve RECIST and/or GCIG cancer antigen 125 (CA125) responses. The confirmed objective response rate (ORR) per RECIST by investigator review was 53.8% (57/106) and the confirmed response by RECIST or GCIC CA-125 was 70.8% (75/106). The confirmed ORR per RECIST by independent review was 41.5% (44/106).

In addition, BRCA wild-type, LOH high patients with relapsed, platinum sensitive ovarian cancer were also shown to derive benefit from rucaparib, with 44% achieving RECIST and/or GCIG CA-125 responses (ARIEL2, Part 1).

Overview of Safety

The US prescribing information (USPI) for rucaparib in the treatment setting is based on 377 patients with advanced ovarian cancer. The most common treatment-emergent adverse events (TEAEs) were nausea, asthenia/fatigue, vomiting, anemia/hemoglobin decreased, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, constipation, decreased appetite, and dysgeusia. *(21)* Commonly experienced Grade 3 or higher TEAEs included anemia/hemoglobin decreased, asthenia/fatigue, and ALT/AST increased.

Integrated Safety Analysis:
Results of a more recent integrated safety analysis for rucaparib treatment in over 900 patients with ovarian cancer who received 600 mg BID rucaparib in either the treatment or maintenance setting showed that the most common TEAEs reported were primarily mild to moderate (Grade 1-2) in severity and included gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, anemia/decreased hemoglobin, ALT/AST increased, decreased appetite, and dysgeusia. The most common TEAEs ≥ Grade 3 included anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine, most commonly occurring. Decreased platelets, neutrophils, leukocytes, lymphocytes, and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib treatment in either the treatment or maintenance settings were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time. Furthermore, no cases met Hy's law criteria for drug-induced liver injury (DILI) and few patients discontinued rucaparib due to ALT/AST elevations. *(22, 23)* Similarly, elevations in creatinine were self-limiting and stabilized over time. Elevated serum creatinine levels resolved upon interruption or discontinuation of rucaparib, were not accompanied by changes in blood urea nitrogen (BUN), and did not lead to discontinuation of rucaparib treatment. *(24, 25)* Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters. Effects on cardiac channel activity in vitro and a comprehensive assessment of the effects of rucaparib on electrocardiogram (ECG) parameters in cancer patients demonstrated a low risk of cardiac effects by rucaparib.

Adverse Events of Special Interest:
Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs), as these events have been observed in patients exposed to cytotoxic chemotherapy (eg, platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation. *(26, 27)* Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib. More information on AESIs for rucaparib is provided in the rucaparib IB.

2.4 Feasibility

This trial will be open to patients with NSCLC regardless of histology (non-squamous (predominantly adenocarcinoma) or squamous cell carcinoma) who enroll on Lung-MAP with deleterious BRCA1/2 mutation and/or LOH high tumors and progression either on or after platinum-based chemotherapy or PD-1/PD-L1 antibodies. Analysis of the TCGA and Foundation Medicine databases suggests that tumors with a LOH ≥ 21% comprise

approximately 16% of squamous cell lung cancer and 9% lung adenocarcinoma. Based on TCGA, 1.4% BRCA 1/2 is common in NSCLC. We note that the **S1400G** sub-study of Lung-MAP is a Phase 2 trial of the PARP inhibitor talazoparib in homologous repair deficient (HRD) squamous cell lung cancer. Based on the TCGA, there is only 4% overlap for LOH high squamous NSCLC and the talazoparib HRRD gene list for **S1400G** sub-study (Figure 3). Similar frequency of overlap was observed in the Foundation Medicine NGS screening data in sqNSCLC from the Lung-MAP program. Patients that overlap will be randomized to either **S1400G** (talazoparib) or **S1900A** (rucaparib) sub-studies. Notably, patients with adenocarcinoma are excluded from **S1400G**, thus there is no overlap in adenocarcinoma patients between the rucaparib and **S1400G** talazoparib sub-study. In summary, with the expected frequency of LOH-positive squamous and adenocarcinoma tumors, we expect robust accrual for this Lung-MAP sub-study as outlined in our accrual estimates.

2.5 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	5	0	0	7
White	34	41	1	2	78
More Than One Race	0	0	0	0	0
Total	37	48	1	2	88

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this sub-study, rucaparib is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances, submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, requests may be submitted to the CTSU website by completing the CTSU Request for Clinical Brochure Form under the sub-study's abstract page > Documents > Pharmacy Tab.

3.1 Rucaparib (Rubraca ®) (NSC 804038) (IND-143217)

a. PHARMACOLOGY

Mechanism of Action: Rucaparib is a potent small molecule inhibitor of poly-adenosine diphosphate (ADP) ribose polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3. Rucaparib also prevents the dissociation of PARP-1 and PARP-2 enzymes from damaged DNA ("PARP trapping"). Inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes can result in increased DNA damage, cytotoxicity, and apoptosis.

b. PHARMACOKINETICS

1. Absorption: The median Tmax was 1.9 hours at the approved recommended dose. The mean absolute bioavailability of rucaparib immediate-release tablet was 36% with a range from 30% to 45%. Following a high-fat meal, the Cmax was increased by 20% and AUC0-24h was increased by 38%, and Tmax was delayed by 2.5 hours, as compared to dosing under fasted conditions. The effects of food were not deemed to be clinically significant; rucaparib may be administered with or without food.

2. Distribution: Rucaparib had a steady-state volume of distribution of 113 L to 262 L following a single intravenous dose of 12 mg to 40 mg rucaparib. In vitro, the protein binding of rucaparib was 70% in human plasma at therapeutic concentrations. Rucaparib preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.83.

3. Metabolism: In vitro, rucaparib had a low metabolic turnover rate and was metabolized primarily by CYP2D6, and to a lesser extent by CYP1A2 and CYP3A4. Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups.

4. Elimination: The mean terminal T1/2 of rucaparib was 25.9 hours, following a single oral dose of 600 mg rucaparib. The apparent clearance ranged from 15.3 to 79.2 L/hour, following rucaparib 600 mg oral twice daily.

c. ADVERSE EFFECTS

1. Adverse Effects:

(Version: November 2, 2020)

Adverse Events with Possible Relationship to rucaparib		
Likely (> 20%)	**Less Likely (4 ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia/decreased hemoglobin	Neutropenia/Neutrophil count decreased	
Thrombocytopenia/ decreased platelets		
GASTROINTESTINAL DISORDERS		
Abdominal pain	Abdominal distension	
Constipation	Dyspepsia	

Adverse Events with Possible Relationship to rucaparib		
Likely (> 20%)	**Less Likely (4 ≤ 20%)**	**Rare but Serious (≤ 3%)**
Diarrhea	Dry mouth	
Nausea	Gastroesophageal reflux disease	
Vomiting	Stomatitis	
GENERAL DISORDERS		
Asthenia/fatigue	Mucosal inflammation	
	Edema peripheral	
	Pyrexia	
INFECTIONS AND INFESTATIONS		
	Nasopharyngitis	
	Upper respiratory tract infection	
	Urinary tract infection	
INVESTIGATIONS		
ALT/AST increased	Blood creatinine increased	
	Blood alkaline phosphatase increased	
	Blood cholesterol increased	
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	Dehydration	
	Hypokalemia	
	Hypercholesterolaemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Musculoskeletal pain	
	Pain in extremity	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED		
		Myelodysplastic Syndrome
		Acute Myeloid Leukemia
NERVOUS SYSTEM DISORDERS		
Dysgeusia	Dizziness	
	Headache	
PSYCHIATRIC DISCORDERS		
	Anxiety	
	Depression	
	Insomnia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	Pneumonitis
	Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	

Adverse Events with Possible Relationship to rucaparib		
Likely (> 20%)	**Less Likely (4 ≤ 20%)**	**Rare but Serious (≤ 3%)**
	Erythema	
	Photosensitivity reaction	
	Pruritus	
	Rash	
VASCULAR DISORDERS		
	Hot flush	
	Hypertension	

Adverse events occurring in < 1%, postmarketing, and/or case reports:

MDS/AML: A review of all reports of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) that have occurred in the entire clinical development program up to 27 June 2020 revealed a total of 25 reports in patients exposed to rucaparib. Nearly every patient who developed MDS/AML reported having experienced multiple/persistent cytopenias prior to the diagnosis of MDS/AML. Events of MDS and AML have also been reported with other PARP inhibitors although the etiology of these events is confounded by prior treatments and the relationship to rucaparib is not clear.

Pneumonitis: Cases of pneumonitis have been reported in patients receiving PARP inhibitor treatment. There have been 10 serious clinical study cases and 7 non-serious clinical study cases reported. Among patients receiving rucaparib, pneumonitis has been reported in approximately 0.1% of patients. There is not a clear mechanistic link between pneumonitis and PARP inhibitor treatment.

For additional information on reporting adverse events of special interest, see Section 16.1f.

2. Pregnancy and Lactation: Based on the finding that rucaparib was embryotoxic at all doses administered in the embryo-fetal development study and the potential of PARP inhibitors to affect spermatogenesis, it is advised that female and male patients of reproductive potential and their opposite sex partners of reproductive potential practice a highly effective method of contraception during and after treatment with rucaparib as specified per protocol. Female patients of childbearing potential and their male partners are advised to practice a highly effective method of contraception during treatment with rucaparib and for 6 months following the last dose of rucaparib. Male patients of reproductive potential and their female partners of childbearing potential are advised to practice a highly effective method of contraception during treatment with rucaparib and for a minimum of 3 months following the last dose of rucaparib. Male patients must not make sperm donations during treatment and for 3 months following the last dose of rucaparib.

3. Drug Interactions:

Rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Concomitant administration of

rucaparib with CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates may alter the pharmacokinetic or pharmacodynamics properties of these concurrent medications. In vitro, rucaparib had a low metabolic turnover rate and was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Caution should be used for concomitant use of strong inhibitors or inducers of these liver enzymes. Rucaparib is a substrate of transporter P-gp and BCRP, a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. Cautions should be taken for concomitant use with substrates and inhibitors of these transporters. See Section 7.2 for details.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

1. Rucaparib 200mg, 250mg, and 300mg immediate-release film-coated tablets will be supplied by Clovis and distributed by NCI Pharmaceutical Management Branch in the US.

   The physical appearances of the tablets are unique in order to ensure proper identification. The 200 mg tablets are blue, round (11 mm) tablets de-bossed with 'C2'. The cosmetic blue film coating is Opadry II containing polyvinyl alcohol, titanium dioxide, polyethylene glycol (PEG)/macrogol, talc, Food, Drug, and Cosmetic Act (FD&C) Blue #1 colorant, brilliant blue for coloring food (FCF) aluminum lake, and FD&C blue indigo carmine aluminum lake. The 250 mg tablets are white, diamond shaped (15 mm × 11 mm) tablets de-bossed with 'C25'. The 300 mg tablets are yellow, oval tablets (16 mm × 8 mm) de-bossed with 'C3'.

f. STORAGE, PREPARATION & STABILITY

1. Rucaparib tablets are provided in high-density polyethylene (HDPE) bottles (60 tablets per bottle) with child-resistant caps and should be stored in the provided containers between 20°C and 25°C, with excursions between 15°C and 30°C permitted. Contact Clovis for temperature excursion information. If a storage temperature excursion or other quality affecting event is identified, promptly return rucaparib tablets to provided containers between 15°C and 30°C and quarantine the supplies. Submit a completed Investigational Product Incident Report Form (See Appendix 18.4) to Clovis for determination of suitability. This form should be submitted within 24 hours after becoming aware of excursion and prior to dosing.

2. Repackaging of rucaparib tablets is not acceptable. Please dispense the original unopened full bottle(s) of rucaparib.

g. NCI-Supplied Agent Ordering and Agent Accountability

   NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP assigned protocol number (**S1900A**) must be used for ordering all CTEP supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form

1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator in this protocol.

No starter supplies may be ordered. Participants must be enrolled and registered to protocol **S1900A** prior to order submission through OAOP.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration (RCR) Help Desk: RCRHelpDes@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB e-mail: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

Supplier: Rucaparib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents.

1. Drug Return and/or Disposition Instruction

   a. Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials

remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

b. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

4.0 STAGING CRITERIA

Patients must have Stage IV or recurrent disease as outlined below (AJCC Cancer Staging Manual, 8th Edition, 2017):

Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma in situ
Squamous cell carcinoma in situ (SCIS)
Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤ 3 cm in greatest dimension

T1 Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

T1mi Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension

T1a Tumor ≤ 1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.

T1b Tumor > 1 cm but ≤ 2 cm in greatest dimension

T1c Tumor > 2 cm but ≤ 3 cm in greatest dimension

T2 Tumor > 3 cm but ≤ 5 cm or having any of the following features:

- Involves the main bronchus regardless of distance to the carina, but without involvement of the carina
- Invades visceral pleura (PL1 or PL2)
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung

T2 tumors with these features are classified as T2a if ≤ 4 cm or if the size cannot be determined and T2b if > 4 cm but ≤ 5 cm.

T2a Tumor > 3 cm but ≤ 4 cm in greatest dimension

T2b Tumor >4 cm but ≤ 5 cm in greatest dimension

T3 Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium, or separate tumor nodule(s) in the same lobe as the primary

T4 Tumor > 7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus,

vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis
M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or malignant pleural or pericardial effusion. nodules or malignant pleural (or pericardial) effusion. **
M1b Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c Multiple extrathoracic metastases in a single organ or in multiple organs

** Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Statistics and Data Management Center in Seattle at 206/652-2267 or LUNGMAPQuestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).**

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 16, 28, or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Sub-Study Specific Criteria

a. Sub-Study Specific Disease Related Criteria/ Laboratory Criteria

1. Patients must be assigned to **S1900A**. **S1900A** biomarker eligibility defined as LOH high and/or deleterious BRCA1/2 mutation is as follows using the FMI tissue- assay:

Biomarker-positive group	Alteration type	Eligible alteration

LOH	Loss of Heterozygosity (LOH)	Genomic LOH ≥ 21%
BRCA	Homologous Recombination Deficiency (HRD)	Deleterious mutations in BRCA1 or BRCA2

2. Patients must not have had prior treatment with any PARP inhibitor, including rucaparib, talazoparib, veliparib, olaparib, or niraparib. For information and a list of PARP inhibitors, please consult the **S1900A** – Poly Polymerase Inhibitors, Scott et al., 2015 JCO ref from the link on the **S1900A** protocol abstract page of the SWOG (http://swog.org) or CTSU (https://www.ctsu.org) websites.

3. Patients must be able to take oral medications.

4. Patients with known ≥ Grade 3 hypercholesterolemia must be ≤ Grade 2 (≤400 mg/dL) within 28 days prior to sub-study registration. (Fasting cholesterols is required to be performed pre-registration only in those patients where clinically indicated.) Note: Use of medication to lower cholesterol is acceptable. Caution should be noted for the use of certain statin drugs. See Section 3.1c.3.

   ≥ Grade 3 hypercholesterolemia ("cholesterol high") is defined by NCI CTCAE v5 as blood cholesterol measurement > 400 mg/dL

b. **Sub-Study Specific Prior/Concurrent Therapy Criteria**

1. Patients must not be planning to receive any concurrent chemotherapy or small molecular or hormonal therapy within 21 days and biologics (e.g. bevacizumab, necitumumab or ramucirumab) or immunotherapy within 28 days prior to sub-study registration and while receiving treatment on this study. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

5.2 Common Eligibility Criteria for all Sub-Studies

a. **Disease Related Criteria**

1. Patients must not have EGFR sensitizing mutations, EGFR T790M mutation, ALK gene fusion, ROS 1 gene rearrangement, and BRAF V600E mutation unless they have progressed following all standard of care targeted therapy.

2. Patients must not have documented evidence of acute hepatitis or have an active or uncontrolled infection.

3. Patients with a known history of HIV seropositivity:

   i. Must have undetectable viral load using standard HIV assays in clinical practice.

   ii. Must have CD4 count ≥ 400/mcL.

   iii. Must not require prophylaxis for any opportunistic infections (i.e., fungal, mAC, or PCP prophylaxis).

iv. Must not be newly diagnosed within 12 months prior to sub-study registration.

b. **Prior/Concurrent Therapy Criteria**

1. Patients must have progressed (in the opinion of the treating physician) following the most recent line of therapy.

2. Patients must not have received any prior systemic therapy (systemic chemotherapy, immunotherapy or investigational drug) within 21 days prior to sub-study registration. Patients must have recovered (≤ Grade 1) from any side effects of prior therapy. Patients must not have received any radiation therapy within 14 days prior to sub-study registration. (See Section 5.2c.2 for criteria regarding therapy for CNS metastases).

c. **Clinical/Laboratory Criteria**

1. Patients must have measurable disease (see **S1900A** Section 10.1) documented by CT or MRI. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in **S1900A** Section 10.1c. Measurable disease must be assessed within 28 days prior to sub-study registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. Non-measurable disease must be assessed within 42 days prior to sub-study registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. See **S1900A** Section 15.0 and **LUNGMAP** Appendix 18.2 for guidelines and submission instructions for required central radiology review. CT and MRI scans must be submitted for central review via TRIAD.

2. Patients must have a CT or MRI scan of the brain to evaluate for CNS disease within 42 days prior to sub-study registration. Patient must not have leptomeningeal disease, spinal cord compression or brain metastases unless: (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment, and prior to registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

3. Patient must not have had a major surgery within 14 days prior to sub-study registration. Patient must have fully recovered from the effects of prior surgery in the opinion of the treating investigator.

4. Patients must have an ANC ≥ 1,500/mcl, platelet count ≥ 100,000 mcl, and hemoglobin ≥ 9 g/dL obtained within 28 days prior to sub-study registration.

5. Patients must have adequate hepatic function as defined by serum bilirubin ≤ Institutional Upper Limit of Normal (IULN) and either ALT or AST ≤ 2 x IULN within 28 days prior to sub-study registration (if both ALT and AST are done, both must be ≤ 2 IULN). For patients with liver metastases,

bilirubin and either ALT or AST must be ≤ 5 x IULN (if both ALT and AST are done, both must be ≤ 5 x IULN).

6. Patients must have a serum creatinine ≤ the IULN OR or calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to sub-study registration:

   Calculated Creatinine Clearance = $\frac{(140 - \text{age}) \times (\text{actual body weight in kg†})}{72 \times \text{serum creatinine*}}$

   Multiply this number by 0.85 if the patient is a female.

   † The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
   * Actual lab serum creatinine value with a minimum of 0.7 mg/ dL.

7. Patients must have Zubrod performance status 0-1 (see **S1900A** Section 10.4) documented within 28 days prior to sub-study registration.

8. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see **S1900A** Appendix 18.1).

9. Pre-study history and physical exam must be obtained within 28 days prior to sub-study registration.

10. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

11. Patients must not be pregnant or nursing. Women of reproductive potential must have agreed to use an effective contraceptive method during the study and 6 months after completion of study treatment. Men of reproductive potential must have agreed to use an effective contraceptive method during the study and 3 months after completion of study treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures during the study and for 6 months after study completion for females and 3 months after study completion for males.

5.3 Specimen Submission Criteria

a. Patients must agree to have blood specimens submitted for circulating tumor DNA (ctDNA) as outlined in Section 15.0.

b. Patients must also be offered participation in banking and in the correlative studies for collection and future use of specimens as described in **S1900A** Section 15.0.

5.4 Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see **S1900A** Section 13.0 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

c. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

6.0 STRATIFICATION FACTORS

Patients will be stratified into two cohorts based on their histology.

Cohort 1: Patients with squamous cell lung cancer.

Cohort 2: Patients with non-squamous cell lung cancer (adenocarcinoma, large cell, NSCLC NOS, mixed histology with any non-squamous component).

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Jonathan W. Riess and Dr. Paul Wheatley-Price at S1900AMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

7.1 Disease Assessment

See Section 9.0 for disease assessment time points. Submit scans as outlined in Section 14.0 and Section 15.0.

Disease Assessment During Treatment
CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.2) must be repeated every 6 weeks (± 7 day window), for the first year regardless of treatment delays, then every 12 weeks (± 7 day window) until disease progression and discontinuation of protocol treatment. The 6 weeks should start from Cycle 1 Day 1.

Pre-study Brain CT/MRI is required 42 days prior to sub-study registration per Section 5.2. If patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated every 12 weeks (± 7 day window) regardless of treatment delays, while on treatment.

Disease Assessment During Off Protocol Treatment, Prior to Progression
After off protocol treatment prior to progression, disease assessments must continue every 12 weeks (± 7 day window) until progression.

If patient has brain metastases at baseline, continue brain CT or MRI scans (same modality as baseline) after off protocol treatment prior to progression, as clinically indicated. For alignment with the protocol and good clinical practice, recommended frequency of brain scans after off protocol treatment (and prior to progression) is at least every 12 weeks, unless more frequent scans are clinically appropriate.

7.2 Precautions

Photosensitivity
Patients should use common precautions when going outside, such as applying sunscreen and/or covering exposed skin with clothing and wearing a hat and sunglasses, as photosensitivity has been observed.

Concomitant Medications
Use caution for concomitant medications that are substrates of CYP1A2, CYP2C9, CYP2C19 and/or CYP3A, and adjust dosage if clinically indicated. If co-administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing the frequency of international normalized ratio (INR) monitoring. Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers. Selection of an alternative concomitant medication is recommended.

Because rucaparib is a strong BCRP inhibitor, concomitant use of drugs that are BCRP substrates (e.g., rosuvastatin) are **not allowed** during the treatment study. See the following url for examples:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2

See Section 3.0 and Appendix 18.5 for additional details.

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)
MDS/AML occurred in patients exposed to rucaparib, including one fatal event of AML. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed.

If AML/MDS is suspected, then patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice. Bone marrow analysis should include a bone marrow aspirate per standard hematologic practice.

Please see Section 8.3 for additional guidance on neutropenia, thrombocytopenia and anemia toxicities.

Embryo-Fetal Toxicity
Rucaparib can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

7.3 Pre-Medication

a. Pre-medication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

7.4 Treatment – **S1900A**

Agent	Dose	Route	Day	Schedule
Rucaparib	600 mg**	Oral	BID	Continuous

* Note: One cycle = 21 calendar days
** Total daily dose = 1200mg

Site and patient instructions can be found in the Intake Calendar (Section 18.6).

7.5 Drug Compliance Documentation

Drug compliance for rucaparib will be recorded by patients in the Intake Calendar (see www.ctsu.org). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Sites utilizing the CIRB must use the Intake Calendar provided.

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Sections 10.2d and 10.2e). *

   * Upon progression, the Request for New Sub-Study Assignment Form may be submitted under the patient's screening protocol (**LUNGMAP** or **S1400**) to receive a new sub-study assignment (see Section 14.4i).

b. Unacceptable toxicity.

c. Treatment delay for any reason > 28 days (or as noted in Section 8.0).

d. The patients may withdraw from the protocol treatment at any time for any reason.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow-Up Period

All patients will be followed until death or 3 years after sub-study registration, whichever occurs first.

Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study, in addition to follow-up on the new sub-study.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Considerations

a. Missed doses are to be omitted rather than made up.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. Once dose is reduced, patients will continue at the new dose. No dose re-escalations are allowed.

d. A maximum of three dose reductions are allowed.

e. The maximum dose delay for any reason is 28 days.

See Section 7.3 for patient instructions.

8.3 Dose Modifications – Rucaparib

Dose modifications should be made based on the observed toxicity, as summarized in the tables below.

DRUG	DOSE LEVEL	DOSE
Rucaparib	Full	600 mg BID
	-1 Level	500 mg BID
	-2 Level	400 mg BID
	-3 Level	300 mg BID
	-4 Level	Discontinue

As discussed above, the most common side effects of rucaparib treatment include gastrointestinal disorders (nausea, vomiting, diarrhea, and constipation), asthenia/fatigue, clinical chemistry elevations (ALT/AST, creatinine, and cholesterol), myelosuppression (decreases in hemoglobin, lymphocytes, platelets, and neutrophils), dysgeusia, and decreased appetite. Modification of rucaparib dose may be a necessary component of AE management, and study specific protocol guidelines for dose modifications should be followed. Dose interruptions, with or without subsequent dose reductions, may help to ameliorate AEs attributed to rucaparib therapy.

Treatment with rucaparib should be held if any of the following are observed and a dose reduction should be considered or implemented.

- Grade 3 or 4 hematologic toxicity (except for lymphocyte count decrease).
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below (Table 2).
- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Table 1: Bone Marrow Suppression Dose Modifications/Interruptions

Toxicity	Dose Modification/Interruption	Toxicity Management
Anemia		
≥ Grade 3	Hold protocol therapy until resolution to ≤ Grade 2. May resume protocol therapy at next lower dose. If dose interruption is >28 consecutive days, permanently discontinue protocol therapy.	If persists >14 consecutive days, or a dependence upon blood transfusion occurs, then complete weekly blood counts until resolution.*
Neutropenia		
≥ Grade 3	Hold rucaparib until resolution to ≤ Grade 2 and resume at lower dose.	For patients with persistent neutropenia that does not stabilize or recover with dose modification, consider additional diagnostic evaluation, including bone marrow examination.*
Thrombocytopenia		
≥ Grade 3	Evaluate for other medications that may induce thrombocytopenia and discontinue/modify these medications if indicated in the opinion of the investigator. Hold rucaparib until resolution to ≤ Grade 1 and resume at lower dose.	For patients with persistent thrombocytopenia that does not stabilize or recover with dose modification, consider additional diagnostic evaluation, including bone marrow examination.*

* If a Grade ≥ 3 anemia, neutropenia, or thrombocytopenia occurs and after 28 days of interruption of rucaparib, these cytopenias have not improved to CTCAE Grade ≤ 2, then patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice. Bone marrow analysis should include a bone marrow aspirate per standard hematologic practice.

Table 2: ALT/AST Elevations Dose Modifications/Interruptions

Toxicity	Dose Modification/Interruption	Toxicity Management
Grade 3	Hold protocol therapy until resolution to ≤ Grade 2. Monitor liver function tests. If resolves to ≤ Grade 2 within 2 weeks, continue protocol therapy at same dose. If persists beyond 2 weeks or bilirubin or alkaline phosphatase is elevated, hold protocol therapy until ≤ Grade 2 and resume at dose reduction. If elevation returns on a second occasion, reduce dose. See Section 2.3 (Overview of Safety) for information on transient elevation that can occur in the first 2-3 weeks.	In the absence of other signs of liver dysfunction: • Monitor liver function tests weekly until resolution to ≤ Grade 2. • Continuation of protocol therapy with elevation of ALT/AST up to Grade 3 is allowed provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.
Grade 4	Hold protocol therapy until values have returned to ≤ Grade 2 or better, then resume rucaparib with a dose reduction.	Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted.

Table 3: Cholesterol Elevations Dose Modifications/Interruptions

Toxicity	Dose Modification/Interruption	Toxicity Management
Grade 3	Hold protocol therapy until values return to ≤ Grade 2(≤400 mg/dL) fasting cholesterol. Then resume rucaparib at same dose.	Consider the use of concomitant treatment with a HMG-CoA reductase inhibitor (commonly known as statin). However, caution should be noted for the use of certain statin drugs. See Section 3.1c.3.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Jonathan Riess and Dr. Paul Wheatley-Price at S1900AMedicalQuery@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

8.5 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of **S1900A** must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Rucaparib

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 21 days (+/- 3 days)					At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [6]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [4]			
PHYSICAL									
History & Physical Exam	X	X	X	X	X	X	X	X [5]	
Weight & Performance Status	X	X	X	X	X	X	X	X [5]	
Intake Calendar [9]		X	X	X	X	X			
Toxicity Notation		X	X	X	X	X	X	X [8]	X [8]
Smoking Status Assessment	X						X		
LABORATORY									
	If labs obtained w/in 14 days prior to tx, tests need not be repeated on C1D1.	Up to 48 hours prior to Day 1 tx							
CBC/Diff/Platelets/ Hgb	X	X	X	X	X	X	X	X [8]	X [8]
Serum Bilirubin	X	X	X	X	X	X	X	X [8]	X [8]
ALT or AST [3]	X	X	X	X	X	X	X	X [8]	X [8]
Alkaline Phosphatase	X	X	X	X	X	X	X	X [8]	X [8]
Cholesterol (fasting)[12]	X (per Sec. 5.1a4)	X	X	X	X	X	X	X [8]	X [8]

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 21 days (+/- 3 days) Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles [4]	At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [6]
Serum Creatinine/Calc CrCl	X	X	X	X	X	X	X	X [8]	X [8]
Serum Pregnancy Test		X [11] (w/in 7 days prior to C1D1)							
X-RAYS & SCANS									
CT or MRI for Disease Assessment [1]	X			X (every 6 wks, ± 7 days)		X (every 6 wks, ± 7 days)		X [5] (every 12 wks, ± 7 days)	
Brain CT/MRI [2]	X				X (every 12 wks, ± 7 days)	X (every 12 wks, ± 7 days)		X (every 12 wks, ± 7 days)	
SPECIMEN SUBMISSION									
ctDNA Whole Blood		X [10]							
Buffy Coat /Plasma for Banking[13]	X (pre-tx)		X	X	X				X (first progression)
TREATMENT (21 day cycle)									
Rucaparib[9]		X	X	X	X	X			

NOTE: Forms are found on the protocol abstract page on the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines on the allowed protocol visits/treatment window as outlined in https://www.swog.org/sites/default/files/docs/2019-07/BestPracticesupdate.pdf. SWOG Best Practices allows for a ± 3 day window for 21-day cycles.

Footnotes for Calendar 9.1 (Rucaparib):

1 CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.2 **S1900A**) must be repeated every 6 weeks (± 7 day window) for the first year, regardless of treatment delays, then every 12 weeks (± 7 day window) until disease progression and discontinuation of protocol treatment. The 6 weeks should start from Cycle 1 Day 1. Submit scans as outlined in Section 14.0 and Section 15.0 **S1900A**.

2 Brain CT or MRI is required per Section 5.2. If patient has brain metastases at baseline, brain scans must use the same modality as baseline and be repeated every 12 weeks (± 7 days) regardless of treatment delays, while on treatment. If patient has brain metastases at baseline, continue brain CT or MRI scans (same modality as baseline) after off protocol treatment prior to progression, as clinically indicated. For alignment with the protocol and good clinical practice, recommended frequency of brain scans after off protocol treatment (and prior to progression) is at least every 12 weeks, unless more frequent scans are clinically appropriate.

3 If ALT/AST elevation of ≥ Grade 3, monitor liver function tests weekly until resolution to ≤ Grade 2. See Section 8.3 Table 2.

4 During continued treatment, items marked under physical and laboratory should be performed prior to every subsequent cycle, unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks (± 7 days) regardless of treatment delays. Treatment and evaluation will continue until any one of the criteria in Section 7.5 **S1900A** is met.

5 After off protocol treatment prior to progression, patients should be followed by repeating indicated studies every 12 weeks or more often as clinically indicated until progression. Disease assessments should continue every 12 weeks until progression.

6 After off protocol treatment after progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for 2 years then at end of 3 years from date of sub-study registration. Note: Patients who enroll on a new sub-study following progression must continue follow-up on this sub-study, in addition to follow-up on the new sub-study.

7 This footnote has been removed.

8 Assessments should continue until resolution of all acute adverse events.

9 The CRA will review the Intake Calendar at the end of each cycle and confirm patient adherence (See Intake Calendar for site and patient instructions in Section 18.6)

10 ctDNA must be collected prior to treatment initiation per Section 15.3. Note: Kits must be ordered and will take up to 3 days to arrive.

11 Women of child bearing potential must have a negative serum pregnancy test within 7 days prior to Cycle 1 Day 1.

12 Pre-Study fasting cholesterol to be performed as clinically indicated per Section 5.1a4. It is acceptable to perform a non-fasting test for subsequent timepoints; however, if the participant experiences a ≥ Grade 3 hypercholesterolemia, a follow-up fasting cholesterol check must be performed. If ≥ Grade 3 hypercholesterolemia is confirmed, proceed to managing the toxicity as outlined in Section 8.3 Table 3.

13 See Section 15.2 for details.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions *(28)*

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. It is strongly recommended that CT slice of 0.5 cm be used. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. It is no longer necessary to distinguish between spiral and conventional CT.

2. Body scans should be performed with breath-hold scanning techniques, if possible.

3. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with stand-alone CT. *The slice thickness of 0.5 cm or less is highly recommended.* If CT scans have slice thickness > 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

4. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

5. 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.

6. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0 cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. 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. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, all potential sites of metastases should be evaluated at each time point rather than following only sites of disease identified at baseline. It is acceptable to image only the areas of the body most likely to be involved with metastatic disease for the tumor type (chest, abdomen, pelvis, and/or bone scan are typical), with the addition of any areas with suspected involvement based upon clinical symptoms. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR)**: Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see 10.2e).

Notes on progression and new lesions:

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

2. FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

3. A previous abnormal target lymph node that became normal and subsequently enlarged in size meeting the criteria for a pathologic and measurable lymph node (a short axis of ≥ 1.5 cm) should be added to the sum of diameters to determine if criteria for progression are met based on target lesions.

4. A previously abnormal non-target lymph node that became normal and subsequently recurred must meet the criteria for progression based on non-target lesions to be considered progression.

5. A normal lymph node at baseline (<1.0 cm) that subsequently becomes pathologic is considered a new lesion and should be considered progression.

6. If a single pathologic lymph node is driving the progression event, continuation of treatment/follow-up and confirmation by a subsequent exam should be contemplated. If it becomes clear that the new lymph node has not resolved, or has increased in size, the date of progression would be the date the new lymph node was first documented.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.
Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in

determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.
4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.
8. Lymph nodes are considered one organ. Only two lymph nodes should be selected as target lesions. Other involved lymph nodes should be assessed and followed as non-target lesions.
9. "Paired" organs, i.e. lungs, kidneys and ovaries, are considered one organ.
10. Pleural-based lung lesions are considered part of the lung in determining target lesions (a maximum of two lung lesions should be selected), whereas pleural effusions/thickening can be reported as a separate site.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Death

From date of sub-study registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 Investigator-Assessed Progression-Free Survival

From date of sub-study registration to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.7 Progression-Free Survival by Central Review

From date of sub-study registration to date of first documentation of progression assessed by central review or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.8 Duration of Response (DoR)

From date of first documentation of response (CR or PR) to date of first documentation of progression assessed by local review or symptomatic deterioration (as defined above), or death due to any cause among patients who achieve a response (CR or PR). Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size with Power Justification

The primary objective is to evaluate the response rate for rucaparib among patients found to have LOH or BRCA positive tumors as summarized in Table 1.

Table 1. Eligibility Biomarkers

Biomarker-positive group	Alteration type	Eligible alteration
LOH	Loss of Heterozygosity (LOH)	Genomic LOH ≥ 21%
BRCA	Homologous Recombination Deficiency (HRD)	Deleterious mutation in BRCA1 or BRCA2

This study will use the Phase II design implemented in biomarker-driven sub-studies within Lung-MAP. The study will evaluate rucaparib among patients with tumors defined to meet the biomarker eligibility criteria defined in Table 1.

Accrual will be stratified into the cohorts by histology as defined in Section 6.0 (squamous and non-squamous histology). The following details pertain to each cohort.

Within a cohort, the accrual goal is 40 eligible and evaluable patients. Patients will be considered evaluable if they receive at least one dose of rucaparib. Assuming that 10% of patients who are enrolled will be not eligible or evaluable retrospectively, the total accrual goal per cohort is 44 patients, for a total of 88 patients in the study.

A design with 91% power and 1-sided 0.05 level type I error would require 40 patients/cohort to rule out an objective response rate (ORR) of 15% or less if the true ORR is 35% or greater. Calculations were performed using the calculators at www.swogstat.org. We note that the exact power and type I error are 93% and 6.6%, respectively.

The expected prevalence of LOH positivity is 16% for Cohort 1 (squamous) and 9% for Cohort 2 (non-squamous). The expected prevalence of BRCA 1/2 is 5.8% for squamous patients and 1.4% for non-squamous patients. The estimated percentage of patients with both LOH+ and BRCA+ cancers is 0.1% for cohort 1 and 1% for cohort 2 resulting in an estimate eligibility rate for the study of 22% for squamous histology NSCLC and 11% for non-squamous NSCLC.

Sites are notified of a patient's sub-study assignment by the SWOG Statistics and Data Management Center (SDMC) after the results of the biomarker testing have been reported to the SDMC. As described in **LUNGMAP** Section 11.0 (the Lung-MAP screening protocol), patients with biomarkers matching only this study will be assigned to this study and sub-study assignment will be based on randomization for patients eligible for multiple biomarker-driven sub-studies. The frequency of patients assigned to this sub-study will

depend on the other biomarker-driven sub-studies actively accruing while this study is accruing and could be less than the percentages eligible for the sub-studies. To account for this, the estimated percentage of screened patients (with successful biomarker testing) assigned to this study is 20% (same for both cohorts).

The expected average monthly accrual rate is 4 patients/cohort per month. We expect the rates to be approximately equal between the cohorts given the history of Lung-MAP focusing on squamous and abundance of competing studies in non-squamous histology, despite the fact that prevalence of squamous histology is about a quarter of all NSCLC. The anticipated duration of accrual is 11 months per cohort.

11.2 Analysis Plan

An interim analysis will take place when 20 patients/cohort are evaluable for response. Evaluability for response is defined based on RECIST 1.1 and accrual is to remain open while patients are being evaluated for response. However, if 20 or more eligible patients/cohort for the first interim analysis have made it to their second disease assessment and the required number of responses to continue past that interim analysis has not been observed, then the accrual to the cohort will be placed in temporary closure until the response status for all patients in the interim analysis set is known.

This interim analysis will only evaluate early stopping for futility. If 2 or fewer responses are observed (within a cohort), this will be considered evidence of futility and the recommendation will be to close the cohort for lack of evidence of efficacy of the regimen. Interim decisions within a cohort will not affect the outcome of the other cohort.

If the study continues to full accrual, the observation of at least 10 responses within a cohort will be considered evidence to rule out the null hypothesis of a 15% response rate within that cohort.

Response rates and associated confidence intervals will be calculated. OS, IA-PFS, and DoR will be estimated using the method of Kaplan-Meier. The Brookmeyer-Crowley method will be used to calculate confidence intervals for median times. With 40 patients, response rates can be estimated within 16% with 95% confidence.

Toxicity will be evaluated among all patients enrolled on the study (combining the squamous and non-squamous cohorts). With 80 patients, any toxicity can be estimated to within 11% with 95% confidence. Any toxicity with at least 5% prevalence has at least a 98% chance of being observed.

Analysis of IA-PFS will take place when 31 IA-PFS events/cohort have been observed. A key secondary objective is an assessment of median IA-PFS (mPFS). If the ORR rate is less than 25%, but the mPFS is at least 4.5 months, this may be considered sufficient evidence to continue to the follow-on Phase III. With 40 patients/cohort this design has 87% power to rule out a mPFS of 3 months or less, if the true mPFS is 6 months, at the 0.05 1-sided level. This is based on using Brookmeyer-Crowley test of null of 3 month mPFS versus alternative of 6 month mPFS with 10 months of accrual and 6 months' follow-up. The observation of an mPFS of at least 4.6 months would be considered evidence to rule out an mPFS of 3 months or less.

12.0 DISCIPLINE REVIEW

12.1 Radiology Review

Central collection is required but review of scans will not be triggered if the study will not be submitted to the FDA for FDA approval of the investigational therapy. Central review of

scans will be triggered only if deemed necessary for FDA evaluation. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in LUNGMAP Section 18.2f.

a. To ensure the highest standards and consistency between different centers, all scans for disease assessment (baseline, interim and end of treatment scans) must be submitted to the National Cancer Institute's National Clinical Trials Network (NCTN) Imaging and RT Quality Assurance Service Core (IROC) in Ohio for centralized review (see **S1900A** Section 15.0).

b. Centralized review will be performed by 3 radiology experts. The scans will be submitted to IROC. IROC will transmit the scans to the reviewers who will transmit the results to the SWOG Statistics and Data Management Center.

c. Details of submission of scans to IROC for centralized review and on the central review process are listed in **S1900A** Section 15.0 and **LUNGMAP** Appendix 18.2.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **LUNGMAP** for registration guidelines.

In order to open Lung-MAP studies at the site, a separate Study Specific Worksheet (SSW) is required to be submitted to the CIRB for the **LUNGMAP** screening protocol and each sub-study.

13.1 Registration Timing

Patients must plan to begin treatment within 10 calendar days after sub-study registration.

13.2 Investigator/Site Registration

For investigator/site registration, please refer to Section 13.2 of the **LUNGMAP** screening protocol. In addition, a Delegation Task Log is required for this sub-study.

Delegation Task Log (DTL):
Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol page on the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see **S1900A** Section 14.3 for details.

14.3 Data Submission Procedures

a. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

b. Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888/823-5923 or by e-mail at mailto:ctsucontact@westat.com.

c. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

d. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

e. Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendar functionality.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS OF **S1900A** REGISTRATION, SUBMIT:

S1900A Eligibility Criteria Form

S1900A Onstudy Form

If needed, also submit:
Radiation Therapy Form
Brain Metastases Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at baseline*

If needed, RT summary and/or planning document*

If needed, radiology report from brain CT/MRI*

*(NOTE: Upload reports via the Source Documentation: Baseline form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease at baseline as specified in **S1900A** Section 15.5

b. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0 **S1900A**

c. WITHIN 15 DAYS AFTER EACH CYCLE (CYCLE = 21 DAYS) OF TREATMENT, SUBMIT:

S1900A Treatment Form

S1900A Adverse Event Form*

S1900A Laboratory Values Form

For Cycle 1 only: Submit the S1900A Pre-Treatment Laboratory Values Form.

*For the last cycle of treatment, include all adverse events occurring within 30 days after the last treatment.

d. WITHIN 15 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF PROTOCOL TREATMENT PRIOR TO DISEASE PROGRESSION (see **S1900A** Section 9.0 for Disease Assessment Schedule), SUBMIT:

Follow-Up Tumor Assessment Form (RECIST 1.1) documenting results of assessment

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in **S1900A** Section 15.5.

e. WITHIN 15 DAYS OF DISCONTINUATION OF TREATMENT, SUBMIT:

Off Treatment Notice documenting reasons for off protocol treatment

Smoking Status Assessment Form

Forms specified in Section 14.4c.

f. ONCE OFF PROTOCOL TREATMENT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1900A** REGISTRATION, THEN AT THE END OF YEAR 3 FROM SUB-STUDY REGISTRATION SUBMIT:

Advanced NSCLC Follow-Up Form

If needed, also submit:
Radiation Therapy Form
Brain Metastases Form

Late Adverse Events (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] adverse event that is possibly, probably, or definitely related to protocol treatment, or a Serious Adverse Event [SAE] of any grade/attribution, that has not been previously reported).

g. WITHIN 15 DAYS OF PROGRESSION/RELAPSE, SUBMIT:

Site(s) of Progression or Relapse Form

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease at follow-up (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit to IROC via TRIAD for Central Radiology Review: Images from scans performed to assess disease as specified in **S1900A** Section 15.5.

h. WITHIN 30 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information and **S1900A** End of Study form. In addition, if the patient was still on protocol treatment, submit materials specified in **S1900A** Section 14.4e or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

i. Data Submission FOR PATIENTS WHO HAVE PROGRESSED AND WISH TO REGISTER TO A NEW SUB-STUDY:

WITHIN 15 DAYS OF PROGRESSION/RELAPSE:

Submit the Request for New Sub-Study Assignment Form under the patient's screening protocol (**LUNGMAP** or **S1400**) in Rave®. Continue follow-up on **S1900A** per Section 9.0. See Section 14.0 of the screening protocol for additional data submission requirements following request for new sub-study assignment.

j. WITHIN 30 DAYS OF MAXIMUM FOLLOW-UP OF 3 YEARS:

S1900A End of Study Form

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **LUNGMAP** Section 5.1 for SWOG Specimen Tracking System (STS) instructions.

15.2 Translational Medicine and Banking (***OPTIONAL FOR PATIENT***)

Specimens for translational medicine and banking (submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the patient:

a. With patient's consent, specimens must be collected and submitted as follows:

1. Buffy Coat and Plasma:

Specimens must be collected at the following times.

- Pre-study (after consenting and prior to treatment initiation on sub-study
  Note: If a patient provided buffy coat and plasma for **LUNGMAP** (see Section 15.0 of **LUNGMAP**) and the blood collection was within 42 days prior to the sub-study registration, then no additional pre-study blood specimen is required.
- Weeks 4, 7, and 10 - Patients that go off protocol treatment are not required to continue to submit specimens.
- First progression after study treatment.

Collect approximately 8-10 mL of blood in EDTA tubes. Blood should be processed within one hour after venipuncture. If immediate processing within this time frame is not possible, then refrigerate (4°C) blood in EDTA tubes. The approximate time from collection to processing should be recorded as part of the patient's source documentation. EDTA tubes must be centrifuged at 800 x g for 10 minutes at 4°C for the collection of plasma. [Note: Sites that do not have a refrigerated centrifuge should spin at room temperature and ensure specimens are placed on ice (regular, not dry) immediately after being drawn and process rapidly.] Using a pipette, transfer the plasma to a 15-mL centrifuge tube. Remove the buffy coat layer (thin white or gray layer of cells between the plasma and red blood cells) and split between two appropriately labeled 2-mL cryovials.

Spin the plasma in the 15-mL centrifuge tube at 800 x g for an additional 10 minutes. Avoiding any pelleted material, pipette the plasma into coded cryovials at 0.5 ml aliquots. Plasma must be clear before freezing; no cells or debris should be present.

Plasma and buffy coat vials must be placed upright in a -80°C freezer immediately after processing to ensure long-term viability.

Frozen plasma and buffy coat specimens should be shipped to the SWOG Biospecimen Bank on dry ice.

b. Specimen Collection, Submission, and Labeling Instructions

Samples for multiple patients may be shipped in batches to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201, at least every 3 months if not more frequently.

For additional information about labeling and shipping instructions for frozen plasma and buffy coat specimens, refer to the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

1. Liquid specimens must be labeled with the following:
   - SWOG patient number
   - Patient initials
   - Collection date (date the specimen was collected from the patient)
   - Specimen type (e.g. blood, serum, etc.)

c. Specimen collection kits are not being provided for this submission; sites must use institutional supplies.

15.3 LUNGMAP ctDNA Research Assay – ctDNA bTMB Peripheral Whole Blood (***REQUIRED FOR PATIENTS prior to treatment initiation***)

Blood specimens will be collected in order to isolate and investigate circulating tumor DNA (ctDNA) and blood tumor mutational burden (bTMB) – a form of fragmented DNA released into patient peripheral circulation specifically from the tumors. Analysis of ctDNA can reveal the presence of tumor-specific mutations and other abnormalities that can serve as biomarkers. The information collected will be limited to tumor-specific abnormalities known or suspected to play roles in tumor evolution. Patient germ-line genetic information will not be collected.

a. Kit Ordering

Immediately after identifying a patient for trial and prior to treatment initiation, sites must contact Foundation Medicine Inc. – Blood Samples, Lab #232, to order kits as follows:

- Call FMI Client Services at 1-888/988-3639 or email request to lung.map@foundationmedicine.com
- Site must identify itself as a participant in the **S1900A** SWOG Lung-MAP sub-study and request the "Lung-MAP ctDNA Clinical Trial Kit."
- Reference the FMI Study ID: FoundationOneLiquidDX-AMC-PRO-20-1496 and Product ID: FMI-P-020
- Provide the following information:
  - Treating physician's name
  - Treating physician's email address
  - Contact name
  - Contact email address
  - Contact phone
  - Address to which kits should be sent
  - Number of kits needed (one per patient per timepoint)

Kits will arrive within 3 days after ordering (excluding weekends and holidays).

Kits will be gray and white in color, read "Foundation Medicine Clinical Trials Kit," and and include four Roche Cell-Free DNA blood collection tubes, collection instructions, FedEx return bags, and pre-printed FedEx airway bills. Blood collection tubes must be used before their expiration date.

b. Timepoints

Collect blood after sub-study registration and prior to treatment initiation.

- Recommended to collect on Cycle 1 Day 1 (prior to treatment) during other labs to lessen patients visits.

  Note: This is a separate requirement for a ctDNA whole blood specimen for all patients registered to **S1900A**, regardless of whether or not there was a ctDNA blood collection for **LUNGMAP**.

c. Specimen Collection and Shipment Instructions

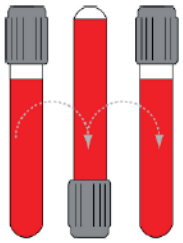
Specimen must be logged via the SWOG Specimen Tracking System.

Step 1: Check special tubes provided in kits to confirm liquid is clear and without cloudiness or crystals.

Step 2: Label tubes with date of collection, patient identifiers as requested on the included labels (patient data of birth can be added as an extra identifier), and sub-study number.

Step 3: Collect four tubes of whole blood (8.5 mL per tube)
- Prevent backflow: tubes contain chemical additives and it is important to avoid backflow into patient
- Collect specimen by venipuncture
- Fill tubes completely (8.5 mL per tube)

Step 4: Remove the tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180° and back, per the figure below.



Step 5: Place specimen into the specimen collection kit.
- Confirm each tube is labeled with the supplied labels indicating the date of collection and two unique patient identifiers (label included in kit).

Step 6: Select "Ship this Shipment and Generate Packing List" in the SWOG Specimen Tracking System to generate the Packing List. A copy of the SWOG Specimen Tracking Packing List must be included in the shipment. Confirm that the tubes are labeled as specified on the Packing List.

Step 7: Preferably on the same day of collection, ship to FMI – Blood Samples, Lab #232 via FedEx overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples. Keep at 43-99° F (6-37° C).

FMI accepts Saturday deliveries. If shipping on a Friday, please overnight shipment and mark for Saturday delivery.

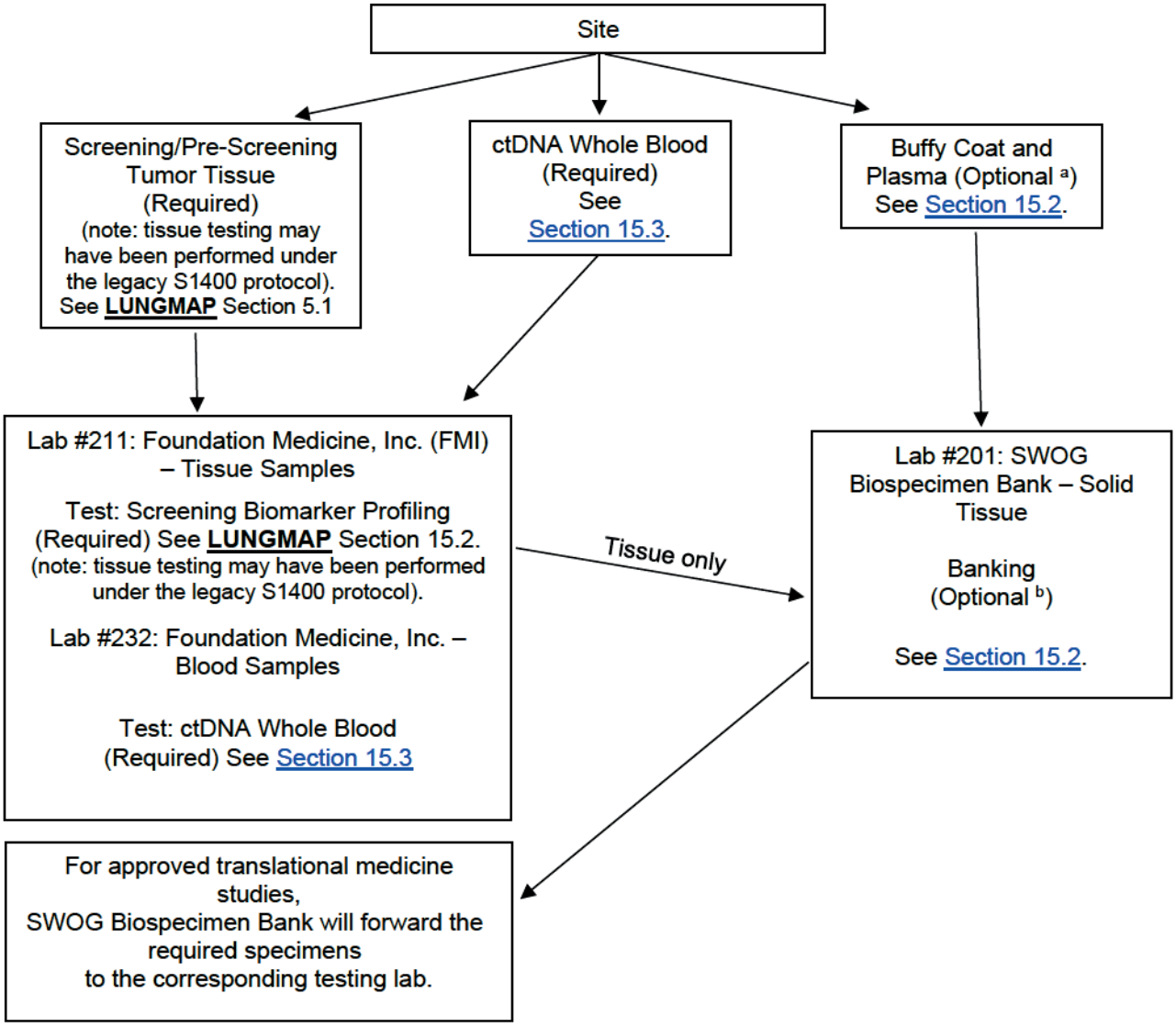
d. Specimen Usage

Whole blood will be collected from each patient as per collection instructions in the dedicated tubes provided in the LUNGMAP ctDNA Research Kit, and shipped at room temperature on the same day of draw, following all indicated directions above. The blood will be processed at FMI; DNA will be extracted and analyzed using a hybrid-capture next-generation sequencing approach optimized for ctDNA extracted from plasma. Alterations in clinically significant cancer genes (oncogenes and tumor suppressor genes) will be identified and quantitated relative to wild-type sequences. Tumor-specific alterations will include point mutations, small insertions and deletions, chromosomal rearrangements and copy number/amplification events in 311 genes (LUNGMAP ctDNA Research Assay). The panel identifies chromosomal rearrangements that result in oncogenic fusions in six genes highly relevant to lung cancer (ALK, EGFR, FGFR3, PDGFRA, RET and ROS1). Data reported will include the specific base substitutions, insertions or

deletions at their mutant allele frequency (the proportion of mutant sequences relative to wild-type sequences, a quantification of gene copy number abnormalities, and the presence of fusions, including the fusion partners and breakpoint information. The ctDNA translational medicine proposal will be submitted as an amendment for CTEP review and approval prior to SDMC review of assay results.

The ctDNA results are for research purposes and will not be shared with the investigator or patient.

15.4 Specimen Flow Diagram



a With patient's consent.

b Remaining tissue will be sent to the SWOG Biospecimen Bank -Solid Tissue, Myeloma and Lymphoma Division, Lab #201, for use of the Translational Medicine studies within any sub-study the patient is enrolled in. SWOG Biospecimen Bank will prepare and ship the required specimens to the appropriate laboratory. The specimen will be kept until there are no additional sub-studies for the patient to enroll in or the tissue is used up, whichever happens first. With patient's consent, any leftover tissue will remain at the SWOG Biospecimen Bank for future exploratory analysis.

15.5 Radiology Review (***REQUIRED***)

CT, PET/CT, and/or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as retrospective central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review at the timepoints specified in Section 7.1.

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging at the timepoints specified in Section 7.1 until progression of disease. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see **LUNGMAP** Section 10.1). Each exam should be performed per Appendix 18.2 of **LUNGMAP**. IROC will perform a QC of the imaging exams.

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinical appropriate considerations.

Central review of scans will not be triggered if the study will not be submitted to the FDA for FDA approval of the investigational therapy. Central review of scans will be triggered only if deemed necessary for FDA evaluation. A detailed description of the central radiology PFS review, including image acquisition parameters and image submission instructions, can be found in Appendix 18.2 of **LUNGMAP**.

b. TRIAD Digital Image Submission

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account (see **LUNGMAP** Section 13.2).
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at:
https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice.

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46.

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312 and the CTEP Investigator's Handbook.

Publication and Industry Contact

The agents supplied by CTEP, DCTD, NCI used in this protocol are provided to the NCI under Collaborative Agreements (CRADA, CTA, CSA) between the Pharmaceutical Companies (hereinafter referred to as "Collaborators") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agents in this study:

a. Agents may not be used for any purpose outside the scope of this protocol, nor can Agents be transferred or licensed to any party not participating in the clinical study. Collaborators data for Agents are confidential and proprietary to Collaborators and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

b. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    1. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the

proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

2. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

3. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

c. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborators, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

d. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

e. Any data provided to the Collaborators for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

f. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborators for advisory review and comment prior to submission for publication. Collaborators will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborators for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:
E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborators. No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Trial Master File

This study is a potential FDA registration study; therefore, all participating sites should be FDA "inspection ready". This entails maintaining a Trial Master File that includes essential documents that may be subject to FDA oversight. A list of essential documents is available on the SWOG website under QA/Audits, https://swog.org/Visitors/QA/Index.asp.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Definition and Purpose

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (FDA, 21 CFR 312.32). See Table 16.1 for definition of a Serious Adverse Event (SAE) and reporting requirements.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org . An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report via CTEP-AERS within the number of calendar days of learning of the event specified in Table 16.1.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

Copies of all adverse event reports submitted to the FDA should be forwarded electronically to CTEPSupportAE@tech-res.com with the protocol number in the subject line.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is rucaparib.

If there is any question about the reportability of an adverse event or if Internet connectivity is please telephone or email the SAE Program Manager at the Operations Office, 210-614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 16.1.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention rucaparib[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a Non-CTEP-IND:**

1. **Group-specific instructions.**

   Supporting Documentation Submission – Within **5 calendar days** submit documentation supporting the CTEP-AERS report to the SWOG Operations Office by fax 210-614-0006. Specific instructions will be sent by email to the reporting site by the SAE Program Manager.

2. The adverse events listed below also require expedited reporting via CTEP-AERS for this trial:

   - All second and secondary malignancies (See Section 16.1g)
   - Any grade of pneumonitis is reportable:
     - pneumonitis
     - interstitial lung disease
     - pulmonary fibrosis
     - acute interstitial pneumonitis
     - alveolitis necrotizing
     - alveolitis
     - hypersensitivity pneumonitis
     - organizing pneumonia

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). For this protocol, second malignancies also require expedited reporting via CTEP-AERS.

   For more information see:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. Supporting documentation must also be submitted to SWOG Operations Office by fax to 210-614-0006.

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Serious Adverse Events to Clovis**

SWOG Operations will forward reports of all serious adverse events and events of overdose (defined as any dose above the protocol-specified dose of rucaparib) associated with an SAE **within 24 hours** of NCI/CTEP receipt of serious adverse event documentation from the study site.

i. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 210-614-0006. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

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18.0 APPENDIX

18.1 New York Heart Association Classification

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.2 Monitoring Plan

For information on the **LUNGMAP** Monitoring Plan, please refer to **LUNGMAP** Appendix 18.2.

18.3 Instructions for the SWOG Biospecimen Bank

Frozen Plasma and Buffy Coat
The SWOG Biospecimen Bank will receive frozen plasma and buffy coat at up to 5 time points per patient. Upon receipt, the Bank will accession, barcode, and Bank specimens in a -80°C freezer.

Formalin-fixed Paraffin-Embedded (FFPE) Tissue
The SWOG Biospecimen Bank will receive FFPE specimens as either blocks or slides/sections at up to 1 timepoint per patient. Upon receipt, the Bank will accession, barcode, and Bank specimens at ambient temperature.

At the end of the study, the Bank will receive notification from the SWOG Statistics and Data Management Center to distribute specimens for testing.

18.4 Investigational Product Incident Report Form

For information on rucaparib storage temperature excursion, please refer to **S1900A** Section 3.1 and submit this form to Clovis within 24 hours after becoming aware of excursion and prior to dosing.

Investigator Initiated Trial Information					
IIT Number:		Investigator:			
Site Number, if applicable:		Site Country:			
Study Staff Name:		Title:			
Email:		Tel:		Report Date:	

Investigational Product Incident Summary		
IP Name: **rucaparib tablets**	**Active IP** Dosage Form and Strength: ☐200mg ☐250mg ☐300mg	**Placebo** Dosage Form and Strength: ☐200mg ☐250mg ☐300mg
Lot No(s): *(i.e H02288A1)*		IP Type: (ex: bottle, blister, vial) **Bottle**

Select type of incident: temperature excursion, lost IP, damaged IP, miscount, or other. Complete one form for each incident.

☐ Lost IP / Damaged Shipment (Shipment # if applicable:_____) ☐ Damaged IP

☐ Miscount ➔ ☐ over-filled ☐ under-filled ☐ Other:_____

Patient ID:	Visit Cycle #	Patient's Current Dose:	Frequency:

Patient Next Visit Date (DD-MMM-YYYY):	
Date Patient Reported incident to the Site (DD-MMM-YYYY):	
Please indicate number of IP tablets/bottles/etc. that were affected:	
Did patient miss any doses? *If yes, please ensure the patient recorded the missed dose in their patient diary, if applicable.*	☐ Yes ☐ No
Do you need urgent resupply due to this event?	☐ Yes ☐ No
Did you attach accompanying documents and/or photos?	☐ Yes ☐ No

☐ Temperature Excursion

Please complete below table for summary of excursion and explanation of event. Check ☑ appropriate boxes.

Excursion Date (DD-MMM-YYYY)	Minimum Excursion Temperature	Maximum Excursion Temperature	Excursion Duration (hours)	Temperature Log Attached?	Was the IP previously involved in another temperature excursion? If yes, please provide date.	
	☐°C ☐°F	☐°C ☐°F		☐Yes ☐ No	☐Yes ☐ No	(DD-MMM-YYYY)

Comments:

☐ N/A *(if no additional comments)*

Signature: _____ **Date:** _____
Email this form to RucaSupply@clovisoncology.com (preferred) **or Fax to + 1 415 276 5777**
THIS SECTION IS TO BE COMPLETED BY CLOVIS PERSONNEL ONLY
Clovis Comment:
Clovis Review Name & Title:
Clovis Signature: _____ **Date:** _____

18.5 Examples of Cytochrome (CYP) Substrates

See Section 7.2 for precautions.

Because lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list for the most up-to-date listing of agents; medical reference texts such as the Physicians' Desk Reference may also provide this information.

Please consult the "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers," which can be found on the U.S. Food and Drug Administration website at See the following FDA links for additional examples of sensitive substrates. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

18.6 Intake Calendar – Rucaparib SWOG Study: **S1900A**

Site Personnel Instructions

- Patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient.
- Ensure that patient clearly understands the guidelines for self-medication.
- Patient should be given enough supply to last until their next study visit.
- Unused drug and/or empty bottles should be returned to the site at the next study visit.
- A new Intake Calendar must be given to a patient with a change in dose or tablet strength. Re-educate the patient regarding their dose schedule as stated below.
- It is recommended that sites contact the patient/caregiver by telephone to confirm dosage adherence in the first few days of Cycle 1 and during the first cycle following any tablet strength change.

Please review the following with the patient:

- Cycle, Start Date and Start Time information with the patient. If possible, have the patient document their first dose in the appropriate calendar box.
- Patient's dose schedule: Rucaparib should be taken twice a day, as close to the same time each day as possible. Provide patient with the instructions on how to document this schedule appropriately.

  Include on the Intake Calendar and review with the patient: dosage, strength of tablets provided, quantity to take at each dose, and tablet description (i.e. blue, round tablet).

  Verify that the tablet strength listed on the bottle label matches the instructions provided to the patient.

  Tell the patient what the tablets will look like based on the strength provided:
  - **200 mg tablets: blue, round shaped tablets, marked with "C2"**
  - **250 mg tablets: white, diamond shaped tablets, marked with "C25"**
  - **300 mg tablets: yellow, oval shaped tablets, marked with "C3"**
- Rucaparib can be taken with or without food.
- How to document vomited, missed, or skipped doses in the specific areas provided.

Cycle: _____ Start Date: _____ Start Day (circle one): Sun M Tu W Th F Sat

Instructions for the patient:
This is a 21-day cycle calendar on which you are to record the number of rucaparib tablets you take each day. You should:

- Take rucaparib 2 times a day at the same time of day as close to 12 hours apart as possible, unless otherwise instructed.
- Take rucaparib with at least 8 oz. (240 mL) of room temperature water with or without food.
- Put the date in the box on the calendar and note the time of both doses for each day.
- Check off if the dose was taken or not
- Swallow the tablet whole; do not chew them prior to swallowing.
- Document any changes to taking the doses in the comments section provided below
  - If you **miss a dose**, take your next dose at your usual scheduled time. Do not take an extra dose to make up for a missed dose.
  - If you **vomit a dose**, do not take an extra dose. Take your next dose at your usual scheduled time.
  - If you **take too much** of rucaparib, call your site personnel listed below.
  - If you develop any side effects, mark this on the calendar on the day you note the effect. Contact site personnel listed below.
- Take medication as directed by study doctor.

Storage:
Store rucaparib tablets should be stored at room temperature (between 15 ºC and 30ºC) in their original container. Keep the medication in their bottles: do not transfer to any other container or share your medication with anyone. Keep out of the reach of children and pets.

Your dose is: _____ (example: 600mg twice daily)

You should take: _____ (number of pills) _____ mg (example: 300 mg, 200 mg or 250 mg).

Description of tablet: _____ (i.e. blue, round tablet)

If you have questions, contact: _____ Telephone: _____

Special Instructions:

Date	Was dose taken?	What time?	# tablets taken (tablet strength)	Comments
Example	**1st dose:** ☑ Yes □ No **2nd dose:** ☑ Yes □ No	8 : 00 (am)/pm 8 : 00 am/(pm)	**1st dose:** 2 (300 mg) **2nd dose:** 2 (300 mg)	
Day1 ____/____/____	**1st dose:** □ Yes □ No **2nd dose:** □ Yes □ No	____:____am/pm ____:____am/pm	**1st dose:** _____ **2nd dose:**_____	

Date	Was dose taken?	What time?	# tablets taken (tablet strength)	Comments
Example	1st dose: ☑ Yes □ No 2nd dose: ☑ Yes □ No	8 : 00 (am)/pm 8 : 00 am/(pm)	1st dose: 2 (300 mg) 2nd dose: 2 (300 mg)	
Day2 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 3 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 4 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 5 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 6 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 7 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 8 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 9 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 10 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 11 ____/____/____	1st dose: □ Yes □ No 2nd dose: □ Yes □ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	

Date	Was dose taken?	What time?	# tablets taken (tablet strength)	Comments
Example	1st dose: ☑ Yes ☐ No 2nd dose: ☑ Yes ☐ No	8 : 00 (am)/pm 8 : 00 am/(pm)	1st dose: 2 (300 mg) 2nd dose: 2 (300 mg)	
Day 12 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 13 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 14 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 15 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 16 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 17 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 18 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 19 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 20 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	
Day 21 ____/____/____	1st dose: ☐ Yes ☐ No 2nd dose: ☐ Yes ☐ No	____:____am/pm ____:____am/pm	1st dose: _____ 2nd dose:_____	

18.7 PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **Rucaparib**. This clinical trial is sponsored by SWOG. This form is addressed to the patient but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Rucaparib interacts with *certain specific enzymes in your liver, certain transport proteins that help move drugs in and out of cells. These enzymes and transport proteins may interact with over-the-counter, herbal, and prescriptions medications.*

- The enzymes in question are *CYP1A2, CYP2C9, CYP2C19, and CYP3A*. Rucaparib blocks drugs that need these enzymes to break down further in the liver. Co-administration of rucaparib with drugs that are CYP1A2, CYP2C9, CYP2C19, and CYP3A substrates may increase risks of toxicities of these drugs.

- Rucaparib also inhibits the function of MATE1, MATE2-K, and OCT1, which are proteins that move drugs in and out of cells/organ. Co-administration of rucaparib with drugs that are substrates of these transport proteins may increase risks of toxicities of these drugs.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Rucaparib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Rucaparib must be used very carefully with other medicines that use certain *liver enzymes or transport proteins to be effective or to be cleared from your system.* Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered *"strong inducers/inhibitors or substrates"* of *CYP450, transport proteins MATE1, MATE2-K, and OCT1. These characteristics may change how rucaparib or other medicine works in your body.*

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Prescription drugs such as metformin (for diabetes), digoxin (for heart conditions), or drugs with narrow therapeutic window like warfarin (or Coumadin, for blood clots).

- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **rucaparib.** This clinical trial is sponsored by the NCI. Rucaparib may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Rucaparib interacts with specific liver enzymes called CYP1A2, CYP2C9/19, and CYP3A, transport proteins (MATE1/2-K, and OCT1) and must be used very carefully with medicines that require these enzymes and transport proteins.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.