Cover Page for Clinical Trials Document posting

Official Title: S1400G, "A Phase II Study of Talazoparib (BMN 673) in Patients with Homologous Recombination Repair Deficiency Positive Stage IV Squamous Cell Lung Cancer)"

NCT Number: 03377556

Version Date: 7/19/19

Description:

S1400 [NCT 02154490] is the parent study to **S1400G** [NCT 03377556].

The **S1400** Lung-MAP study is considered one study under one IND consisting of:

- S1400 Version Control Protocol
- S1400 Main Screening Protocol Component
- Multiple Sub-Studies (or sub-protocols) Components

Each component is contained in its own separate document.

S1400G is one of these components. Each "component" consists of the protocol document and its associated informed consent document(s). Since each screening and sub-study component operates independently from the other components contained in Lung-MAP, each has its own version date and NCT number. This is due to the complexity of the study and how it must be entered into different computer programs.

S1400G: HRRD – TALAZOPARIB (BMN 673)

A BIOMARKER-DRIVEN MASTER PROTOCOL FOR PREVIOUSLY TREATED SQUAMOUS CELL LUNG CANCER

A PHASE II STUDY OF TALAZOPARIB (BMN 673) IN PATIENTS WITH HOMOLOGOUS RECOMBINATION REPAIR DEFICIENCY POSITIVE STAGE IV SQUAMOUS CELL LUNG CANCER (LUNG-MAP SUB-STUDY)

NCT #02154490

This is a potential FDA registration study. There will be additional centralized and on-site monitoring conducted in addition to routine audits. Sites must also maintain a study specific Trial Master File for this study.

Lung-MAP and its sub-studies are being conducted under SWOG IND 119672 and CIRB. The Lung-MAP 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. However, for regulatory purposes, all Lung-MAP sub-study protocols should be processed as a single study for Continuing Review.

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study 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 sub-tab under the Regulatory tab.) 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) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at 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 to the SWOG 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 on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

For patient eligibility questions contact the SWOG Statistics and Data Management Center by phone or email:

206/652-2267
S1400question@crab.org

For treatment or toxicity related questions contact S1400GMedicalquery@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 contact ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Web site is located at https://www.ctsu.org.

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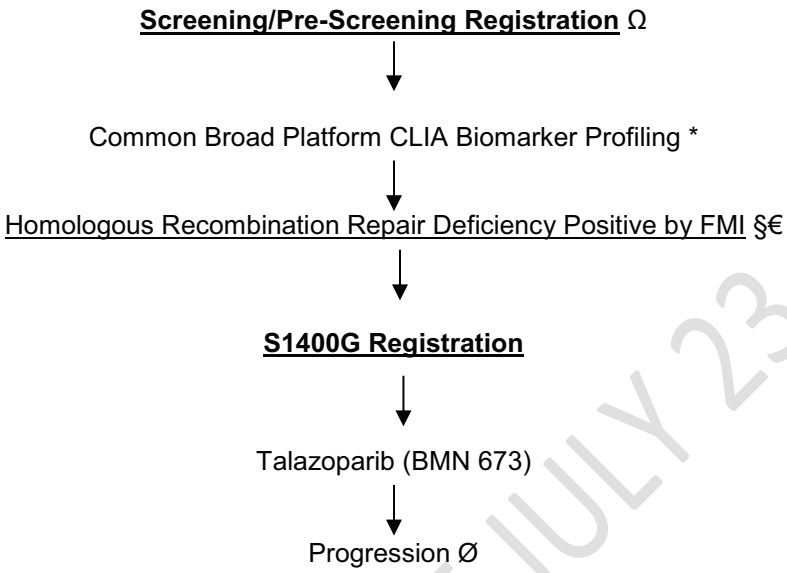

Ω See **S1400** Section 5.1 for screening/pre-screening registration information.

* Archival formalin-fixed paraffin-embedded (FFPE) tumor, fresh core needle biopsy if needed

€ Notification of sub-study assignment will be provided by the SWOG Statistics and Data Management Center (see Section 11.0 in **S1400** for details).

§ See Section 5.0 for the definition of Homologous Recombination Repair Deficiency Positive by FMI criteria.

Ø Upon progression (as defined in Section 10.2d), patients may be eligible for another sub-study. The new sub-study assignment will be determined by the SWOG Statistics and Data Management Center (see Section 14.4).

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1.0 OBJECTIVES

The objective of **S1400G** is to evaluate talazoparib (BMN 673), a poly (ADP) ribose polymerase (PARP) inhibitor, in Homologous Recombination Repair Deficiency (HRRD) positive patients. **S1400G** will utilize a broad definition of HRRD-positivity for eligibility (Foundation Medicine [FMI] criteria as defined in **S1400G** Sections 5.0 and 11.1). However, the primary analyses will be performed using a more restricted definition of HRRD-positivity (Medivation [MDVN] criteria; defined by alterations in ATM/ATR/BRCA1/BRCA2/PALB2 genes; see also **S1400G** Section 11.1).

1.1 Primary Objectives

The primary objective is to evaluate the overall response rate (ORR) (confirmed and unconfirmed, complete and partial) with talazoparib (BMN 673) in HRRD MDVN-positive patients.

1.2 Secondary Objectives

a. To evaluate investigator assessed progression-free survival (IA-PFS) and overall survival (OS) associated with therapy in HRRD MDVN-positive patients.

b. To evaluate ORR, IA-PFS, and OS in HRRD FMI-positive patients.

c. To evaluate ORR in HRRD MDVN-negative/ HRRD FMI-positive patients.

d. To evaluate the frequency and severity of toxicities associated with talazoparib (BMN 673) in HRRD FMI-positive patients.

1.3 Translational Medicine Objectives

a. To assess if the HRD score is associated with clinical outcomes (response, PFS, OS) in HRRD FMI-positive patients treated with talazoparib (BMN 673).

b. To assess if the level of PARP protein expression determined by immunohistochemistry is associated with clinical outcomes (response, PFS, OS) in HRRD FMI-positive patients treated with talazoparib (BMN 673).

c. To characterize pharmacokinetic properties of talazoparib (BMN 673).

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2.0 BACKGROUND

DNA Damage Repair (DDR) and Synthetic Lethality:

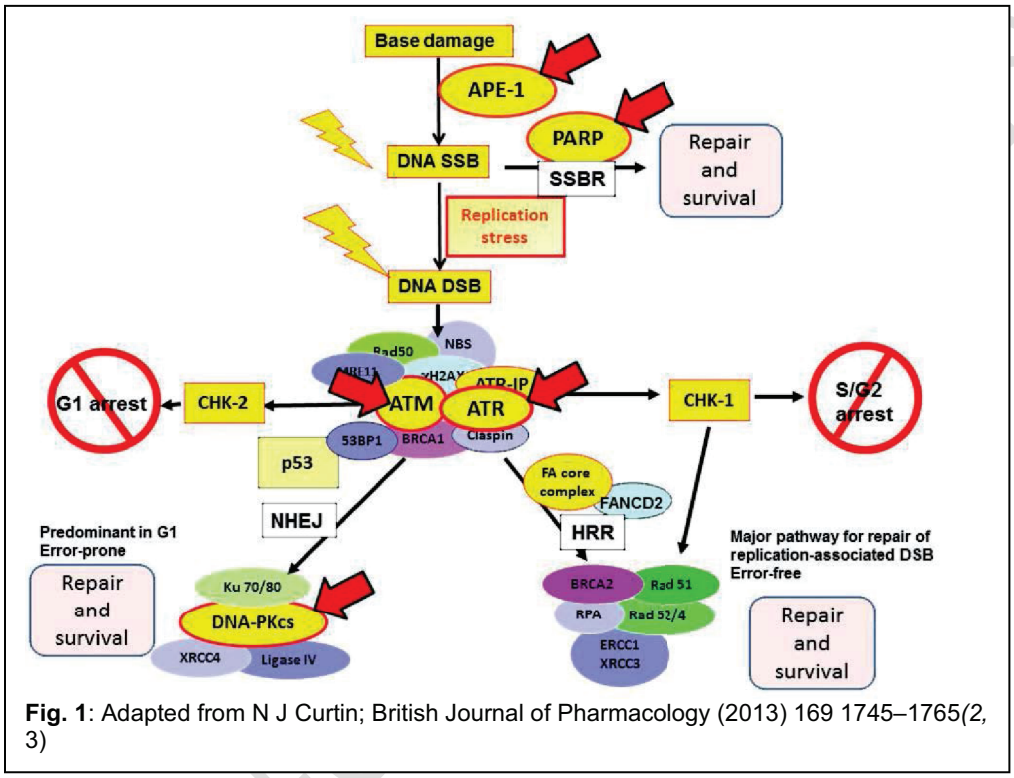

Fig. 1: Adapted from N J Curtin; British Journal of Pharmacology (2013) 169 1745–1765*(2,* 3)

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)* This network of protein-protein interaction that affects the repair of damaged DNA, in addition to maintaining cell viability, may also confer survival advantage. 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. Examples of these include MMR defects resulting in Lynch syndrome and HRR deficiency resulting from BRCA1, BRCA2, and FANCD2 gene mutations commonly described in breast, ovarian, AML, head and neck and esophageal cancers. 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 very 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

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highly lethal double strand breaks. The inability of the cells to repair this highly lethal 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. *(2)* It is now recognized that besides BRCA1 and BRCA2, synthetic lethality can also be induced when genetic mutations affect other critical components of HRR. There is robust preclinical evidence that alterations in other components of HRR such as RAD51, RAD54, DSS1, RPA1, NBS1, ATR, ATM, CHK1, CHK2, PTEN, FANCD2, FANCA, or FANCC are associated with synthetic lethal consequence when cells bearing such alterations are exposed to PARP inhibitors. *(3)*

PARP Inhibition and Predictive Biomarkers of Efficacy:

PARP is highly expressed in lung cancer including the squamous lung cancer subtype. *(4)* High expression of specific DNA repair enzymes may occur as a compensatory response to abnormalities involving other specific components of the DDR pathways. Because such compensatory changes suggest an overreliance of the cancer cells on the compensatory pathway, it is reasonable to expect that inhibitors of PARP will be particularly effective as therapeutic options in tumors with high PARP expression. This was amply demonstrated in small cell lung cancer (SCLC) where cell line sensitivity to a PARP inhibitor showed strong correlation with baseline expression of proteins involved in DNA repair pathways. *(5)* More importantly, the specific DDR pathway component whose alteration induced the compensatory overexpression of PARP in these tumors may also serve as a predictive biomarker of PARP inhibitor therapy. In preclinical models of SCLC, the combination of a PARP inhibitor with cytotoxic chemotherapy resulted in improved anticancer activity of the cytotoxic chemotherapy in vitro and in vivo. *(6)* Interestingly, the potentiating effect of PARP inhibitors appeared to be most pronounced in cell lines that are more sensitive to platinum. Supporting clinical data from ovarian cancer patients also showed significant differences in the efficacy of single agent PARP inhibitor therapy in platinum sensitive versus platinum refractory ovarian cancer. Although there is currently no well-validated predictive biomarker of platinum sensitivity in any type of cancer, the duration of clinical benefit following frontline platinum-based doublet chemotherapy is a strong predictor of platinum sensitivity. This is reflected by the current practice standard of re-treating SCLC patients who are progression free for ≥ 6months with the same platinum-based therapy at the time of progression. Similar definition is employed in ovarian cancer patients where platinum sensitivity is determined by the duration of benefit derived from this class of therapy.

The NHEJ is the salvage pathway for the repair of double strand breaks in cells with compromised HRR. An intact NHEJ is necessary for the expected synthetic lethality of PARP enzyme inhibition in the background of HRD. Therefore, cancer cells with HRD and concomitant deleterious mutations in the components of the NHEJ pathway (DNA-PKcs, Ku-70, Ku-80, XRCC4, Ligase IV, 53BP1) lose their susceptibility to synthetic lethality when treated with a PARP inhibitor, so-called synthetic viability. *(7,8,9)* Consequently, patients whose tumor manifests such genetic profile of concomitant HRR and NHEJ deficiency are unlikely to derive clinical benefit. There is, however, insufficient clinical evidence on which to base a decision whether or not such patients should be excluded from studies evaluating the clinical efficacy of PARP inhibitor therapy.

Prevalence of HRR Deficiency in Lung Cancer:

The Cancer Genome Atlas (TCGA) Data: Frequency of deleterious alterations (deletions and mutations and copy number variations) in non-small cell lung cancer (NSCLC) has been analyzed using the publicly available mutation data from the TCGA on the cBioPortal database (http://www.cbioportal.org/). *(10,11)* Squamous lung cancer is among the top 10 cancers with frequent alterations in HRR pathway genes. Specifically, there were deleterious genetic alterations involving BRCA1 and BRCA2 genes in 14% of cases. Overall, approximately 27% of cases of squamous lung cancer harbored a genetic alteration in at least one of the genes encoding the critical components of the HRR pathway. It is thus reasonable to anticipate that cancer cells harboring genetic alterations in any of these genes would have a greater probability of being HRR-deficient. We therefore reasonably expect that such tumors will be susceptible to the synthetic lethal

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effect of PARP inhibitor therapy and will be appropriate for targeted therapy using a PARP inhibitor. It is noteworthy that genetic alterations involving different HRR genes were generally mutually exclusive indicating reliance of the tumor on one or the other of these pathway components. Moreover, there was no impact of these genetic alterations on patient survival.

Homologous Recombination Deficiency (HRD) Score: HRD score, a tissue based genomic assay, was developed in an attempt to facilitate the identification of patients likely to respond to platinum agents and PARP inhibitors. HRD score is a DNA-based assay based on whole genome tumor loss of heterozygosity (LOH) profiles (HRD-LOH score), telomeric allelic imbalance (HRD-TAI score), (or large-scale state transitions (HRD-LST score). *(1213,14)* It provides a comprehensive signature for HRR deficiency. All 3 scores are highly correlated with defects in BRCA1/2 in breast or ovarian cancer and are associated with sensitivity to platinum agents. HRD score is currently being explored as an integrated biomarker in several clinical trials of PARP inhibitors. In a pilot retrospective study using surgical resections and biopsies from lung cancer cases, HRD was assessed on 18 cases of adenocarcinomas and 10 cases of squamous cell carcinomas of the lung. The assay yielded HRD scores of 2–17 and 3–15 in adenocarcinomas and squamous cancers respectively. Using a cutoff of ≥10 to differentiate high versus low HRD, up to 50% of NSCLC (8 of 18 and 6 of 10 cases of adenocarcinomas and squamous cancers, respectively) were noted to have high HRD scores. (Myriad Genetics; confidential data on file). This proprietary HRD assay is able to dichotomize cancers into platinum-sensitive and insensitive based on the HRD score. Prior evaluation in breast cancer patients showed that breast tumors with high HRD scores are more sensitive to platinum agents given as a neoadjuvant therapy. *(15)* Preclinical and clinical work also showed a strong correlation between platinum sensitivity and susceptibility to PARP inhibitor therapy. We therefore hypothesize that patients with high HRD scores will be particularly vulnerable to talazoparib (BMN 673). This hypothesis will be tested posthoc as one of the secondary objectives in this study.

Platinum Sensitivity in Squamous Cell 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. *(16,17,18)* Additionally, platinum sensitivity shows significant association with clinical benefit of PARP inhibitors in ovarian cancer and in SCLC patients. *(19,20,21)* There is limited clinical evidence regarding the impact of frontline platinum sensitivity on clinical outcome or efficacy of salvage therapy in squamous lung cancer. *(22)* Retrospective and single institution studies suggested that patients with platinum-sensitive NSCLC achieved better outcome with salvage targeted therapy. *(23)* The clinical value of platinum sensitivity in predicting the benefit of post progression salvage therapy and specifically,

PARP inhibitor, for squamous lung cancer is therefore worthy of study and will be appropriate to investigate under the framework of this prospective sub-study. Similar to the broad classification in ovarian cancer, we will characterize all enrolled patients according to the platinum-sensitivity definition in ovarian cancer as follows *(24)*:

i. Platinum-refractory - lack of objective response and or progression during the course of frontline platinum-based chemotherapy.

ii. Platinum-resistant - objective response to platinum-based chemotherapy with disease relapse occurring within six months of the last round of chemotherapy (*i.e.* platinum free interval ≤ 6months counting from the last date of administration of the platinum agent).

iii. Platinum-sensitive - initial response to platinum-containing chemotherapy and a platinum free interval > 6 months (i.e., counting from the last date of administration of the platinum agent).

Talazoparib (BMN 673) is a PARP inhibitor designed to have an improved therapeutic index relative to existing PARP inhibitors in development. BMN 673 is a novel, high purity, orally available, single enantiomer, tosylate compound.

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Nonclinical Studies:

Talazoparib (BMN 673) is a highly potent and specific inhibitor of PARP 1 and 2 with activity in tumor cell lines bearing DNA repair deficiencies. *(25)* Talazoparib (BMN 673) inhibits PARP in vitro at a lower concentration (IC50=0.57 nM) than ABT 888 (IC50=4.73 nM), AG14447 (IC50=1.98 nM), or olaparib (IC50=1.94 nM). In addition to inhibition of PARP enzymatic activity, talazoparib (BMN 673) also shows highly potent PARP trapping activity. (26,27) In non-clinical studies, PARP trapping was demonstrated to be the dominant activity of PARP inhibitors to kill cancer cells. *(28)* As a result, talazoparib (BMN 673) exerted single-agent synthetic lethality of BRCA 1 and 2 and PTEN deficient cell lines with superior potency vs. PARP inhibitors with less PARP trapping activity. *(29)* In BRCA2 negative Capan 1-cells, talazoparib (BMN 673) was more potent as a single agent than ABT-888 (10,000 times), AG14447 (609 times) and olaparib (259 times) in inhibiting PARP activity. *(30)*

In animal models with tumors that bear mutations in HRR genes, potent anti-tumor activity was observed at oral daily doses < 1000 mcg/kg/day. Complete suppression of BRCA1-deficient tumor growth in the MX1 model was achieved in a 3-month study when dosed at 165 mcg/kg bid. *(31,32)* Similarly, suppression of PTEN-deficient tumor growth (i.e., LNCap [prostate] and MDA-MB-468 [mammary] tumor cells) was achieved in xenotransplant experiments with talazoparib (BMN 673) dosed at 330 mcg/kg once daily for 28 consecutive days. *(33)*

The oral bioavailability, calculated from the ratio of area under the concentration-time curve (AUC) following oral administration relative to the AUC following intravenous (IV) administration (AUCoral/AUCIV), was > 46.4% in rats and > 60.1% in dogs based on single dose comparisons. The compound was metabolically stable. The mean terminal half-life (t1/2) of talazoparib (BMN 673) at various doses in rats and dogs ranged from 20.5 to 51.5 hours and 60.9 to 91.2 hours, respectively, which allows for once daily dosing. Pharmacokinetic studies have been performed in rats and dogs. Steady state concentrations were reached by day 15 in rats and by day 20 in dogs using once daily administration of talazoparib (BMN 673). Comparing day 15 and 28 with day 1 for all dose levels in dogs, AUC and Cmax increased from day 1 to day 15 to day 28 (Refer to Investigators Brochure). *(34)*

Five-day repeat dose toxicity and toxicokinetic (TK) studies with 28-day recovery were conducted in rats and dogs. In dogs (the most sensitive species), talazoparib (BMN 673) was administered at dose levels of 3, 10, 30, 100 mcg/kg/day over 5 consecutive days. Severe pancytopenia was observed in dogs treated at the two highest dose levels (30 and 100 mcg/kg/day). At these doses, the mean (or median) reticulocyte nadir occurred on day 6 and the platelet and WBC nadirs on day 11. These changes were reversed in the group treated at 30 mcg/kg/day on Days17-18 (i.e., 12-13 days after the last dose of the drug). Mortalities occurred in animals given 100 mcg/kg/day due to bacterial septicemia secondary to bone marrow hypocellularity and lymphoid organ depletion on Day 12-13. Coagulation parameters were unaffected. After repeat-dose administration of daily oral BMN 673 in dogs for 5 days, the highest non-severely toxic dose (HNSTD) was 30 mcg/kg/day (Refer to Investigators Brochure). *(35)*

Twenty-eight-day repeat dose toxicity and TK studies with 28-day recovery were also conducted in rats and dogs. In dogs (the most sensitive species), talazoparib (BMN 673) was administered at dose levels of 0, 0.5, 1.5, 5, and 10 mcg/kg/day over 28 consecutive days. Talazoparib (BMN 673) related signs included hematology findings in males and females given 5 or 10 mcg/kg/day such as mildly lower red cell mass, mildly to moderately lower platelet and absolute reticulocyte counts, and minimally to mildly lower white blood cell counts with a generalized decrease in all leukocytes. All of these signs reversed or were reversing by the end of the recovery phase. After repeat-dose administration of daily oral talazoparib (BMN 673) in dog for 28 days, the HNSTD was 10 mcg/kg/day.

Thirteen-week repeat dose toxicity and TK studies with 28-day recovery were also conducted in rats and dogs. In dogs, talazoparib (BMN 673) was administered at dose levels 1.5, 5 and 10 mcg/kg/day. Talazoparib (BMN 673)-related signs included hematology findings in males and

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females given 10 mcg/kg/day such as mildly to moderately lower red cell mass, platelet counts and absolute reticulocyte counts and minimally to mildly lower white blood cell counts. All of the hematology findings related to bone marrow depletion were reversed by the end of the recovery phase. After repeat-dose administration of daily oral talazoparib (BMN 673) in dog for 28 days, the HNSTD was 10 mcg/kg/day (Refer to Investigators Brochure). *(36)*

In conclusion, the main nonclinical findings of early hematological changes, and subsequent bone marrow and lymphoid organ depletion as well as focal necrosis after repeat administration of talazoparib (BMN 673) are in accordance with the mechanism of action and the exposure/distribution pattern. These findings were reversible and the decreased reticulocyte, platelet, red blood cell (RBC) and WBC counts were sensitive and early markers of target organ toxicity. Decreases in hematology parameters were used to clinically monitor safety. The mutagenic potential of talazoparib (BMN 673) was assessed in accordance with ICH S2 (R1) with in a battery of genotoxicity studies. Talazoparib (BMN 673) was not mutagenic in a bacterial reverse mutation assay. Consistent with genomic instability resulting from its primary pharmacology, talazoparib (BMN 673) was clastogenic in an in-vitro chromosomal aberration assay and in an in-vivo micronucleus assay, indicating potential for genotoxicity in humans. (Refer to Investigators Brochure). (37)

Effects in Humans:

Two clinical studies are completed and three studies are ongoing at the time of this update (31 March 2015).

- Food Effect (673-103, completed): this completed Phase 1, randomized crossover study evaluated oral Talazoparib (BMN 673) bioavailability in 18 healthy adult volunteers who received a single 500-µg dose of Talazoparib (BMN 673) after an overnight fast and a high-fat, high-calorie meal in a standard 2x2 crossover design. Although food delayed Talazoparib (BMN 673) absorption (prolonged Tmax and reduced Cmax), food did not affect overall extent of absorption (similar AUC0-t and AUC0-∞ values under fed and fasted conditions). Single oral doses of 500 µg Talazoparib (BMN 673) were safe and well tolerated in healthy male volunteers.
- Hematological Malignancies (PRP-002, completed): this completed Phase 1, two-arm, open-label study evaluated talazoparib (BMN 673) in 33 patients with advanced hematological malignancies (acute myeloid leukemia, 21; myelodysplastic syndrome, 4; chronic lymphocytic leukemia, 4; mantle cell lymphoma, 4). Although single-agent talazoparib (BMN 673) was relatively well tolerated in patients with advanced hematologic malignancies, no further study of single-agent talazoparib (BMN 673) in this indication is planned.
- Advanced Solid Tumors (PRP-001, ongoing): This ongoing Phase 1/2 study initiated on 3 January 2011 is a single-arm, open-label study to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of talazoparib (BMN 673) in patients with advanced tumors with DNA-repair pathway abnormalities, particularly those associated with BRCA- and PTEN-dysfunction (NCT01286987). The initial cohort of patients was treated with 25 µg talazoparib (BMN 673) once daily. The dose was successfully escalated to 1000 mcg daily in a continuous dosing schedule in the expansion cohort. As of 18 April 2014, a total of 105 patients (74 female, 31 male) were enrolled in the study. An updated report of the study presented at the 2014 ASCO annual meeting showed that talazoparib (BMN 673) has single agent anti-tumor activity in patients with advanced previously treated SCLC, as well as in ovarian and breast cancer patients with deleterious germline mutations of BRCA1 and 2. *(38)* The SCLC patient cohort achieved a RECIST response rate of 10%, clinical benefit rate (CR,PR,SD ≥ 16 weeks) of 25% with a median duration of response of 13.7 weeks (95% C.I.: 12.0 – 15.3 weeks) and median progression-free survival of 11.1 weeks (95% C.I. 3.1 – 13.0 weeks). The cohort of patients with germline BRCA mutant breast cancer had a response rate of 44%, clinical benefit rate (CR, PR, SD ≥ 24 weeks) of 72% for a median duration of response measured at 32.0 weeks (95% C.I.: 19.9 – 40.3 weeks) and median progression-free survival of 32.1 weeks (95% C.I.: 13.1 – 43.4 weeks). Similarly, 12 of 25 (48%) evaluable patients with ovarian

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cancer harboring a germline BRCA mutation achieved RECIST response rate. The clinical benefit response rate (CR, PR, SD ≥ 24 weeks): was 82% for a median duration of response of 26.9 weeks (95% C.I.: 15.9 – 28.1 weeks) and median progression-free survival of 32.9 weeks (95% C.I. 28.1 – 40.4 weeks). The clinical activity of talazoparib (BMN 673) as a single agent, as observed in this early phase clinical trial in terms of duration of response and PFS noted, appears quite promising. Talazoparib (BMN 673) was generally well tolerated with the most common drug-related toxicities being myelosuppression, mild to moderate fatigue, nausea and alopecia. The severity and frequency of adverse events appears to be similar in patients with advanced previously treated SCLC. *(39)*

PK data from Part 1 of PRP-001, through Cycle 1 showed that plasma concentrations of talazoparib (BMN 673) increased in a dose-dependent manner, with most patients obtaining steady-state plasma concentrations by the end of the second week of daily dosing. As indicated by log-linear concentration-time profiles on Day 1 and Day 35 (not shown), talazoparib (BMN 673) elimination appeared to follow biphasic kinetics. PK of talazoparib (BMN 673) was similar in the expansion phase across all tumor types evaluated at the 1000 mcg dose level.

- Breast Cancer (673-201, ABRAZO; NCT02034916, ongoing): this ongoing Phase 2, open-label, two-stage, two-cohort study evaluates talazoparib (BMN 673) in patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations. Patients are enrolled in one of two study cohorts: (1) platinum responders, or (2) patients with at least three prior chemotherapy regimens who received no platinum for metastatic disease.
- Breast Cancer (673-301, EMBRACA, NCT01945775, ongoing), initiated on 30 October 2013. This ongoing Phase 3, open-label, randomized, parallel-group study evaluates Talazoparib (BMN 673) in patients with HER2 non-amplified breast cancer and with germline BRCA mutations who have received prior chemotherapy for locally advanced or metastatic breast cancer. In a 2:1 ratio, patients are randomized to receive Talazoparib (BMN 673) or one of four protocol-specified, physician's choice therapies (capecitabine, eribulin, gemcitabine, or vinorelbine).

As of 30 November 2014, 219 patients have received at least one dose of talazoparib (BMN 673) in five BioMarin-sponsored studies. Cumulatively, there have been 152 SAEs reported. The most common system organ classes for SAEs have been infections and infestations (38 events in 27 patients), blood and lymphatic disorders (20 events in 16 patients), respiratory, thoracic, and mediastinal disorders (20 events in 19 patients), and GI disorders (19 events in 14 patients). The most commonly reported SAEs, by preferred term, have included febrile neutropenia (9 events in 8 patients), neutropenic sepsis (8 events in 4 patients), pleural effusion (7 events in 6 patients), and disease progression (6 events in 6 patients). All but 16 of these 152 SAEs were assessed by investigators as not related to treatment with talazoparib (BMN 673). These SAEs are consistent with progression of underlying disease or known identified risks of myelosuppression.

Adverse events occurring in at least 10% of patients in the pooled study population of PRP-001, PRP-002, 673-103, and 673-301 have included: fatigue, nausea, anemia, constipation, diarrhea, vomiting, thrombocytopenia, cough, pyrexia, headache, neutropenia, alopecia, decreased appetite, abdominal pain, back pain, dyspnea, pain in extremity, arthralgia, and dizziness. Adverse reactions have not worsened with continued therapy at the same or reduced dose.

Based on its mechanism of action, preclinical activity and PK and toxicity profiles, talazoparib (BMN 673) is a promising investigational agent and appropriate for further evaluation as an anticancer therapy particularly in tumors with demonstrated or potential defects in DNA repair pathways, such as BRCA deficiency and other genetic alterations that confer homologous recombination deficiency.

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3.0 DRUG INFORMATION

Investigator Brochures

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

For this sub-study, talazoparib (BMN 673) 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.

3.1 Talazoparib (BMN 673) (NSC 771561) (IND-119672)

a. PHARMACOLOGY

Mechanism of action: talazoparib (BMN 673) is a highly potent and specific inhibitor of PARP1 and 2 with activity in tumor cell lines bearing DNA repair deficiencies. PARP inhibition induces synthetic lethality in tumor cells bearing mutations in the genes encoding BRCA1 and BRCA2, both of which are key components in the pathway of repair for DNA double-strand breaks. Treatment with a PARP inhibitor results in cell cycle arrest and apoptosis.

b. PHARMACOKINETICS

1. Absorption: Absorption of talazoparib (BMN 673) is rapid and peak concentrations were generally achieved 1 to 8 hours post dose. At steady state, the mean Cmax was 21 ng/mL, the mean plasma trough concentration (Cmin) was 3.72 ng/mL, the mean AUC was 202 ng●h/mL, and the mean peak-to-trough ratio was approximately 6. Food delays absorption of talazoparib (BMN 673), but has no effect on the extent of absorption.

2. Distribution: Protein binding of talazoparib (BMN 673) is 78.7% in human plasma. The apparent volume of distribution (V/F) decreases with increasing doses. At 1000 mcg/day, the mean V/F is 415 L. After repeated administration at 1000 mcg/day, talazoparib (BMN 673) accumulated approximately 2.4-fold relative to a single dose.

3. Metabolism: Overall, talazoparib (BMN 673) is largely cleared via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation.

4. Elimination: Elimination follows biphasic kinetics, with a mean half-life ranging from 52.9 to 229 hours. Renal excretion is a major elimination pathway for unchanged parent talazoparib (BMN 673). Following oral administration, 44 to 90.6% of the dose was recovered in the urine as unchanged parent drug.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of

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events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 553 patients.* Below is the CAEPR for talazoparib (BMN 673).

Version 2.3, June 7, 2019[1]

Adverse Events with Possible Relationship to Talazoparib (BMN 673) (CTCAE 5.0 Term) [n= 553]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
		Febrile neutropenia
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
Diarrhea		
	Dyspepsia	
	Mucositis oral	
Nausea		
		Typhlitis
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
	Pain	
INFECTIONS AND INFESTATIONS		
	Infection[2]	
INVESTIGATIONS		
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy
		Myelodysplastic syndrome

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Adverse Events with Possible Relationship to Talazoparib (BMN 673) (CTCAE 5.0 Term) [n= 553]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS		
	Dizziness	
Headache		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3] Neuropathy peripheral may include both Peripheral sensory neuropathy and Peripheral motor neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

Adverse events reported on talazoparib (BMN 673) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that talazoparib (BMN 673) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Atrial flutter; Sinus bradycardia
GASTROINTESTINAL DISORDERS - Abdominal distension; Flatulence; Intra-abdominal hemorrhage; Small intestinal obstruction; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; General disorders and administration site conditions - Other (accidental overdose); Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure; Sinusoidal obstruction syndrome
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (glioblastoma multiforme); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastatic breast cancer); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastases to meninges)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Intracranial hemorrhage; Nervous system disorders - Other (neuropathy peripheral)3; Nervous

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system disorders - Other (nonserious axonal sensorimotor polyneuropathy); Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Insomnia; Psychiatric disorders - Other (mental status changes)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Oropharyngeal pain; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disorder)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Rash maculo-papular
VASCULAR DISORDERS - Thromboembolic event

Note: Talazoparib (BMN 673) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation:

Studies in pregnant animals to evaluate the effect of talazoparib (BMN 673) on pregnancy have not been performed. Women of childbearing potential and non-sterilized males who are sexually active with a female partner should use highly effective contraceptive measures during and for at least 45 days after completion of treatment.

Studies in lactating animals to evaluate the effect of talazoparib (BMN 673) have not been performed. It is not known whether talazoparib (BMN 673) is excreted in human milk. Therefore, breastfeeding should be stopped during talazoparib (BMN 673) treatment.

3. Drug Interactions:

Talazoparib (BMN 673) does not inhibit or induce CYP450 isoenzymes. Therefore, drug-drug interactions related to CYP450 inhibition or induction are unlikely to be clinically significant.

Talazoparib (BMN 673) is a substrate for P-gp and BCRP, and plasma talazoparib (BMN 673) concentrations may increase or decrease when coadministered with P-gp or BCRP inhibitors or inducers, respectively. Guidelines for concomitant use of talazoparib (BMN 673) with inhibitors or inducers of P-gp or inhibitors of BCRP are as follows:

- Use of strong P-gp inhibitors (e.g., dronedarone, quinidine, ranolazine, verapamil, ketoconazole, itraconazole), P-gp inducers (e.g., rifampin, tipranavir/ritonavir), or BCRP inhibitors (e.g., elacridar [GF120918]) should be avoided.

Caution should be used for coadministration of other P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, felodipine, lopinavir, quercetin), P-gp inducers (e.g., avasimibe, carbamazepine, phenytoin, St John's wort), or BCRP inhibitors (e.g., cyclosporine, eltrombopag, and gefitinib).

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

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e. HOW SUPPLIED

1. Talazoparib (BMN 673) is supplied by Medivation Inc. and distributed by PMB.

   Talazoparib (BMN 673) is a capsule formulation comprised of a blend of talazoparib (BMN 673) tosylate drug substance and silicified microcrystalline cellulose filled into a hypromellose capsule. It is supplied as 1000 mcg (opaque pale-pink, size 4) and 250 mcg (opaque white, size 4) capsules supplied in 30-count high-density polyethylene (HDPE) bottles with induction-sealed closures.

f. STORAGE, PREPARATION & STABILITY

1. Store talazoparib (BMN 673) at room temperature (15-30 ºC; 59-86 ºF). Contact supplier for temperature excursion information.

   Talazoparib (BMN 673) is considered a cytotoxic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment. Patients should be advised that oral anticancer agents are toxic substances and that (other than the patient) caregivers should always use gloves when handling capsules.

2. Repackaging of talazoparib (BMN 673) capsules is acceptable if the same type of bottle is used when repackaging from the original bottle. The required bottle must be made of high density polyethylene resin (HDPE), be white, provide a moisture barrier, and be child proof.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Study specific supplies will be provided to sites once a patient has been enrolled. Starter supplies will not be provided. Pharmaceutical Management Branch (PMB) policy requires that drug 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 (**S1400G**) must be used for ordering all CTEP supplied investigational agents. The eligible 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.

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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.

2. Drug Handling and Accountability

   a. 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 NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov).

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug return and/or disposition instruction

   a. All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), 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 expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.

4. Contact Information and Useful Links

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time or by email: PMBAfterHours@mail.nih.gov.

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration (RCR) Help Desk: RCRHelpDesk@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 IB Coordinator: IBCoordinator@mail.nih.gov
- PMB e-mail: PMBAfterHours@mail.nih.gov

4.0 STAGING CRITERIA

See Section 4.0 of **S1400** for Staging Criteria.

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5.0 ELIGIBILITY CRITERIA

Patient must meet the eligibility criteria in Section 5.0 of **S1400G** to be eligible for **S1400G**. If the patient does not meet the sub-study specific eligibility criteria listed in Section 5.1 and Section 5.2 of **S1400G**, but meets the common sub-study criteria listed in Section 5.3 of **S1400G**, submit the **S1400** Request for Sub-Study Reassignment Form for sub-study reassignment.

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 SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or S1400question@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 Disease Related Criteria

a. Patients must be assigned to **S1400G**. **S1400G** biomarker eligibility defined as Homologous Recombination Repair Deficiency (HRRD) Positive is as follows.

Biomarker-positive group	Alteration type	Eligible alteration
HRRD by FMI [a]	truncating mutation, frameshift deletions, indels missense and nonsense mutations predicted to have functional consequence in any of the specified genes	Mutation in any one of the following critical HRR pathway genes: ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCF, FANCM, NBN (NBS1), PALB2, RAD51, RAD51B (RAD51L1), RAD54L, RPA1

[a] Homologous Recombination Repair Deficiency by Foundation Medicine Inc., criteria.

b. Patients must not have had prior exposure to any agent with a PARP inhibitor (e.g., veliparib, olaparib, rucaparib, niraparib, talazoparib [BMN 673]) as its primary pharmacology. For information and a list of PARP inhibitors, please consult the **S1400G** – Poly Polymerase Inhibitors, Scott et al., 2015 JCO ref from the link on the **S1400G** protocol abstract page of the SWOG (http://swog.org) or CTSU (https://www.ctsu.org) websites.

c. Patients must have achieved stable disease, a partial response, or a complete response at their first disease assessment after initiating first-line platinum-based chemotherapy. Patients determined to have progressed (in the opinion of the treating physician) at their first disease assessment are not eligible.

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5.2 Sub-Study Specific Clinical/Laboratory Criteria

a. Patients may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of talazoparib (BMN 673) (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or active peptic ulcer disease). Patients must not have active small or large intestine inflammation such as Crohn's disease or ulcerative colitis (within 12 months of sub-study registration).

b. Patients must be able to take oral medications. Patients must be able to swallow capsules whole without crushing or altering them in any way.

c. Patients must not be taking, nor plan to take while on protocol treatment, strong P-gp inhibitors, P-gp inducers, or BCRP inhibitors (see Section 3.1c.3 for list of medications).

d. Patients must agree to have blood specimens submitted for pharmacokinetic analysis as outlined in Section 15.3.

5.3 Common Eligibility Criteria for all Sub-Studies

a. Patients whose biomarker profiling results indicate the presence of an EGFR mutation or EML4/ALK fusion are not eligible. Due to existence of approved therapies the biomarker exclusion rules are as follows:

Gene	Alteration type	Ineligible Alteration
EGFR	Substitution	L858R, T790M, A289V, G719A, S768I, G719C, R108K, G598V, R222C, L62R, L861Q, P596L, V774M
	Indel	non-frame shifting insertions or deletions between amino acids 740 and 780, in exons 19 and 20, transcript NM_005228
	Fusion	None
	Amplification	None
ALK	Substitution	None
	Indel	None
	Fusion	EML4-ALK, CLIP4-ALK, CLTC-ALK, KIF5B-ALK, NPM1-ALK, RANB2-ALK, STRN-ALK, TFG-ALK
	Amplification	None

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

c. 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 5.3e for criteria regarding therapy for CNS metastases).

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d. Patients must have measurable disease (see 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 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 Sections **S1400G** 15.0 and **S1400** 18.1c for guidelines and submission instructions for required central radiology review.

e. 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.

f. Patient must have fully recovered from the effects of surgery at least 14 days prior to sub-study registration.

g. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

h. 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.

i. 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).

j. Patients must have a serum creatinine ≤ the IULN OR measured 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:

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

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 0.8 mg/dl.

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

l. 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

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activity without discomfort), unstable angina pectoris, and myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia (see **S1400** Section 18.1).

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

n. Patients with a known history of HIV seropositivity:

1. Must have undetectable viral load using standard HIV assays in clinical practice.
2. Must have CD4 count ≥ 400/mcL.
3. Must not require prophylaxis for any opportunistic infections (i.e., fungal, mAC, or PCP prophylaxis).
4. Must not be newly diagnosed within 12 months prior to sub-study registration.

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

p. 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.

q. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. 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.

r. As a part of the OPEN registration process (see **S1400** Section 13.4 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.

s. 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).

t. 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.

u. Patients must also be offered participation in banking for future use of specimens as described in **S1400G** Section 15.0.

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6.0 STRATIFICATION FACTORS

Not applicable.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Drs. Taofeek K. Owonikoko and Lauren A. Byers at S1400GMedicalQuery@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 Pre-Medication and Supportive Care

Premedication 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.

7.2 Treatment – **S1400G**

Talazoparib (BMN 673)

a. **Talazoparib**

Agent	Dose	Route	Day	Schedule*
Talazoparib (BMN673)	1000 mcg	Oral	Daily	Continuous

* NOTE: A cycle of treatment is 21 days. Disease assessment must occur every 6 weeks. Treatment will continue until any of the criteria in Section 7.4 is met.

Patients should be instructed to swallow talazoparib (BMN 673) capsules whole and not to chew them prior to swallowing. Talazoparib (BMN 673) can be taken with or without food. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day (preferably in the morning).

Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.

Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.

Patients who inadvertently take one extra dose during a day must be instructed to skip the next day's dose.

On days of clinic visits when PK samples are to be drawn, talazoparib (BMN 673) should be taken at the clinic after completion of pre-dose sampling and assessments; on these PK sample dates, the clinic visit should be scheduled for approximately the same time of day that the dose is typically taken. Patients who forget and take their dose may have PK sampling visit rescheduled, if possible. The collection time of PK blood draws and drug administration must be recorded.

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7.3 Drug Compliance Documentation

Drug compliance for talazoparib (BMN 673) will be recorded by patients on the Intake Calendar. 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. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.4 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 **S1400** Request for New Sub-Study Assignment Form may be submitted to receive a new sub-study assignment (see Section 14.0).

b. Unacceptable toxicity.

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

d. The patient may withdraw from this study at any time for any reason.

7.5 Discontinuation of Treatment

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

7.6 Follow-Up Period

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

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov) All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

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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.

8.3 Dose Modifications – Talazoparib (BMN 673)

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

DRUG	DOSE LEVEL	DOSE
Talazoparib BMN 673	Full	1000 mcg/day
	-1 Level	750 mcg/day
	-2 Level	500 mcg/day
	-3 Level	250 mcg/day
	-4 Level	Discontinue

In patients receiving talazoparib (BMN 673) at 1000 mcg/day via continuous daily dosing in the Phase 1 trial (the MTD), the most common toxicities at this dose were fatigue (37%), anemia (35%), nausea (32%), thrombocytopenia (21%), alopecia (20%) and neutropenia (16%). Grade 3 or 4 AEs were reported in 32 (45%) patients, with the most frequent being anemia (23%), thrombocytopenia (18%) and neutropenia (10%).

Table 1: Renal Impairment Dose Modifications

Toxicity	**Dose Modification**
Grade 3	No hold on treatment required, treatment may continue at next lower dose
Grade 4	Hold protocol treatment until resolution to $\leq$ Grade 2, treatment may then resume at the next lower dose

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Table 2: Dose Modifications Based on Hematologic or Nonhematologic Toxicity
Note: No dose modifications are required for any grade lymphopenia.

Toxicity	Dose Modification
Grade ≤ 2 toxicity (other than liver test abnormalities)	No dose modification. NOTE: If the toxicity persists at Grade 2 for ≥ 7 days, reduce dose to the next lower dose.
Grade 3 nonhematologic toxicity (other than liver test abnormalities)	Hold protocol treatment until resolution to ≤ Grade 1 or baseline, treatment may then resume at the next lower dose. Supportive care should be implemented as appropriate (e.g., anti-emetics, anti-diarrheal agents).
Grade 3 hematologic toxicity	Hold protocol treatment until resolution to ≤ Grade 1 or baseline, treatment may then resume at the next lower dose. Supportive care should be implemented as appropriate (e.g., growth factor support, blood products).
Grade 4 nonhematologic toxicity (other than liver test abnormalities)	Hold protocol treatment until resolution to ≤ Grade 1 or baseline, treatment may then resume at the next lower dose. Supportive care should be implemented as appropriate (e.g., anti-emetics, anti-diarrheal agents).
Grade 4 hematologic toxicity	Hold protocol treatment until resolution to ≤ Grade 1 or baseline, treatment may then resume at the next lower dose. Supportive care should be implemented as appropriate (e.g., growth factor support, blood products).

Table 3: Liver Test Abnormalities That Require Dose Modifications

Baseline AST or ALT Value	Elevation	Dose Modification and Toxicity Management
≤ 3 × ULN	> 5 × ULN to ≤ 8 × ULN	Hold protocol treatment pending investigation into alternative causes of drug-induced liver injury (DILI). The patient should be followed for possible DILI. Resuming treatment, at one dose level reduction if no prior dose reduction otherwise resume at same dose, may be considered if an alternative cause for the impaired liver tests (i.e., ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to ≤ Grade 1. The decision to resume treatment should be discussed and agreed on unanimously by the patient, treating investigator, and Study Chair. Following rechallenge, patients should be closely monitored for signs and symptoms of hepatitis, and/or abnormal liver test results. If signs or symptoms recur with rechallenge, study drug should be permanently discontinued and removed from protocol treatment. If an alternative cause for the impaired liver tests cannot be found, permanently discontinue and remove from protocol treatment. **See Table 4 for evaluations.**
> 3 to ≤ 5 × ULN	> 8 × ULN	
Baseline Total Bilirubin Value	**Elevation**	
≤ 1.5 × ULN	> 3 × ULN	

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Study drug should be discontinued permanently if ALL of the following 4 criteria are met (i.e., potential severe DILI/Hy's Law case):

1. AST or ALT increases to ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 and ≤ 5 × ULN)

2. Total bilirubin increases to > 2 × ULN and/or INR > 1.5

3. Alkaline phosphatase (ALP) value does not reach 2 × ULN

4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to:
    - Hepatobiliary tract disease
    - Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, parvovirus)
    - Congestive heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
    - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
    - Alcoholic hepatitis
    - Non-alcoholic steatohepatitis (NASH)
    - Autoimmune hepatitis
    - Wilson's disease and hemochromatosis
    - Alpha-one antitrypsin deficiency

If an alternative cause for hepatotoxicity is identified or if the liver test abnormalities do not reach the specified severity, it is recommended, but not required that study drug be withheld or permanently discontinued, as appropriate for the safety of the patient based on the patient population and/or severity of the hepatotoxicity or event.

All patients in whom study drug is withheld (either conditionally or permanently) due to a potential DILI are to undergo a period of "close observation" until the liver test abnormalities return to baseline or normal values. The evaluations listed in Table 4 are recommend, but not required to be performed.

Table 4: Liver Monitoring After Events Meeting Hy's Law Criteria or Suggesting Potentially Severe Drug-Induced Liver Injuries

Results	**Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests**
After the initial liver test abnormality	Within 24 hours
If AST or ALT ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 and ≤ 5 × ULN), and total bilirubin > 2 × ULN or INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 and ≤ 5 × ULN) and total bilirubin and/or INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

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As DILI is a diagnosis of exclusion, it is important to initiate investigation of alternative causes for abnormal liver tests; this may include consultation with a hepatologist. The Study Chair should be contacted for questions regarding adequate follow-up tests.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Drs. Taofeek K. Owonikoko and Lauren A. Byers at S1400GMedicalQuery@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 the **S1400G** must be reported to the Operations Office, Study Coordinator and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

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9.0 STUDY CALENDAR

9.1 Talazoparib (BMN 673)

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Subsequent Cycles β			At Off Tx	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15			
PHYSICAL																			
History & Physical Exam	X				X			X			X			X			X	X	
Weight & Performance Status	X				X			X			X			X			X	X	
Disease Assessment Ω	X							XΩ						XΩ				XΩ	
Toxicity Notation	X				X			X			X			X			X	Xđ	Xđ
Smoking Status Assessment	X																X		
LABORATORY																			
CBC/Diff/Platelets/Hgb	X	X ℘	X	X	X			X			X			X			X	Xđ	Xđ
Total Serum Bilirubin	X	X ℘	X	X	X			X			X			X			X	Xđ	Xđ
ALT and AST	X	X ℘	X	X	X			X			X			X			X	Xđ	Xđ
Alkaline phosphatase	X	X ℘	X	X	X			X			X			X			X	Xđ	Xđ
Serum Creatinine/Calc CrCl	X	X ℘	X	X	X			X			X			X			X	Xđ	Xđ
Albumin ¥	X																		
X-RAYS AND SCANS																			
CT or MRI for Disease Assessment Ω	X							XΩ						XΩ				XΩ	
Brain CT/MRI	X													X♦				X♦	
Image Submissions Σ	X							X						X				X	
SPECIMEN SUBMISSION																			
Tissue for Banking																			X§
Blood for Banking †	X				X			X			X								Xð
Blood for PK α		X			X			X			X								

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REQUIRED STUDIES	PRE-STUDY	Cycle 1 Wk 1	Cycle 1 Wk 2	Cycle 1 Wk 3	Cycle 2 Wk 4	Cycle 2 Wk 5	Cycle 2 Wk 6	Cycle 3 Wk 7	Cycle 3 Wk 8	Cycle 3 Wk 9	Cycle 4 Wk 10	Cycle 4 Wk 11	Cycle 4 Wk 12	Subsequent Cycles β Wk 13	Subsequent Cycles β Wk 14	Subsequent Cycles β Wk 15	At Off Tx	Off Tx Follow-Up Prior to Prog Δ	Off Tx Follow-Up After Prog √
TREATMENT																			
Talazoparib (BMN 673) (21-day cycle)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.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 as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes for Calendar 9.1 (Talazoparib [BMN 673]):

Ω CT or MRI (the same method used at prestudy to meet the eligibility criteria in Section 5.3 of **S1400G**) must be repeated every 6 weeks (± 7 day window) for the first year regardless of treatment delays, then every 3 months 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 5.3. If the patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated every 12 weeks (+/- 7 days) while on treatment.

℘ If the pre-study tests are obtained within 14 days prior to treatment, the tests need not be repeated on Cycle 1 Day 1.

¥ Results of these tests do not determine eligibility but are recommended prior to sub-study registration.

Σ Submit scans as outlined in Section 14.0 and Section 15.0 of **S1400G.**

β During continued treatment, items marked under physical and laboratory should be performed at every subsequent cycle, unless otherwise noted. Disease assessments and image submission are to take place every 6 weeks (± 7 days).
Treatment and evaluation will continue until any one of the criteria in Section 7.4 of **S1400G** is met.

Δ After off treatment prior to progression, patients should be followed by repeating indicated studies every 3 months or more often as clinically indicated until progression. Disease assessment should continue every 3 months until progression.

√ After off 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.

§ With patient's consent, an additional research biopsy within 1 month after the time of first progression among patients who had a response to talazoparib (BMN 673) (in the opinion of the treating physician) must be collected (see Section 15.0 of **S1400G)**.

† With patient's consent additional research blood draws will be collected (see Section 15.0 of **S1400G**).

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

ð Blood for Banking specimen must be collected at first progression after study treatment (see Section 15.0 of **S1400G**).

α Blood samples for pharmacokinetic analysis will be collected at 3 timepoints on Day 1 of Cycles 1, 2, 3 and 4. The predose sample will be collected ≤ 30 minutes prior to dosing; the two postdose samples will be collected at ≥ 30 minutes after dosing and ≥ 2 hours after the first postdose sample (see Section 15.3 of **S1400G**).

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10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

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.

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. 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. Note: Lymph nodes that have a short axis < 1.0 cm (10 mm) are considered non-pathological and should not be recorded or followed. 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 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. Body scans should be performed with breath-hold scanning techniques, if possible.

2. 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 conventional CT.

   NOTE REGARDING DIAGNOSTIC QUALITY:

   CT – Computed Tomography Imaging

   In order for a CT to be of diagnostic quality to be used in determining measurable disease, the slice thickness needs to match the protocol Section 10.0.

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Recommended Scan mode:	Multi-detector and/or helical
Contrast Enhancement:	IV and oral contrast unless contraindicated
Slice Section thickness:	maximum 5mm, preferable 2.5mm or less
Slice Increment:	continuous or overlapping sections; no gaps
Imaging Region:	Thoracic inlet through adrenal glands (and appropriate scans if disease exists elsewhere)
Image Matrix size:	512 × 512 or better
Image Reconstruction / Filter:	Institutional standard

If a CT scan is performed with a slice thickness greater than 5 mm then lesions must be twice the slice thickness. If any PET/Spiral CT is used at baseline where the CT is of diagnostic quality, follow-up scans can be done by a spiral CT.

If any PET/Conventional CT is used at baseline where the CT is of diagnostic quality, follow-up scans can be done by conventional CT.

Institutions will have to submit radiology reports documenting that the CT used in PET/CT is of diagnostic quality. No other methods of assessments are interchangeable.

MRI – Magnetic Resonance Imaging
MRI can be performed using a 1.5 or 3.0 T field strength. If a MRI is performed instead of a CT, the MRI can be performed according to institutions clinical standard of care protocols with slice thickness of no more than 5mm (in transverse).
If an MRI scan is performed with a slice thickness greater than 5 mm, then lesions must be twice and above the slice thickness.

PET/CT – Positron Emission Tomography with FDG
When a FDG PET/CT is performed, the emission scans should be started in the range of 60 – 75 min after FDG injection, otherwise use your institution protocols. It is necessary for follow up scans that they are performed in an **identical way** to the baseline with the same PET/CT scanner and a variation in timing of no more than +/- 10 min. Preferably, schedule the patient for both baseline and follow-up scans at the same time of day (AM or PM) to improve reproducibility.

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

4. 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.

5. 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 0.0cm should be recorded.

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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, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in the appropriate sub-study specific section.

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 Section 10.2e).

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

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. 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.

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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.

g. 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.

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.

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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 six 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 (or date of screening/pre-screening registration if patient never enrolls in a sub-study) 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 (IA-PFS)

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

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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

The objective of **S1400G** is to evaluate talazoparib (BMN 673), a poly (ADP) ribose polymerase (PARP) inhibitor, in Homologous Recombination Repair Deficiency (HRRD) positive patients. **S1400G** will utilize a broad definition of HRRD-positivity for eligibility (Foundation Medicine [FMI] criteria). However, the primary analyses will be performed using a more restricted definition of HRRD-positivity (Medivation [MDVN] criteria; defined by alterations in ATM/ATR/BRCA1/BRCA2/PALB2 genes;)

This study will employ Design #2 the Seamless Phase II followed by Phase III design as described in **S1400** Section 11.2a. A complete description of the statistical design and analysis plan is included in Section 11.0 of **S1400**. This section includes details specific to **S1400G**.

11.1 Primary Objective and Biomarker Prevalence

Eligibility for **S1400G** (HRRD FMI-positive) and definition of the primary analysis population (HRRD MDVN-positive is defined as the presence of any of the following mutations.

Biomarker group	Alteration type	Eligible alteration
HRRD FMI-positive	truncating mutation, frameshift deletions, indels missense and nonsense mutations predicted to have functional consequence in any of the specified genes	ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCF, FANCM, NBN (NBS1), PALB2, RAD51, RAD51B (RAD51L1), RAD54L, RPA1
HRRD MDVN- positive		ATM, ATR, BRCA1, BRCA2, PALB2

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The expected prevalence of HRRD FMI-positivity is 15%. However, after accounting for the prevalence of other sub-study biomarkers, the expected frequency of patients assigned to **this sub-study** is 13.5% (based on simulation using the randomization ratios as defined in **S1400** Section 11.1). It is further estimated that the subset defined by ATM, ATR, BRCA1, BRCA2, and PALB2 (here called HRRD MDVN-positive) has a prevalence of 8% or about 53% of the HRRD FMI-positive group. This proportion is an estimate and is affected by the actual prevalence of other sub-study biomarkers and affected by the closure and activation of other sub-studies.

Phase II Design: S1400G will follow the Phase II design from Design #2: Seamless Phase II followed by Phase III (see Section 11.2 of **S1400**) among patients defined to be HRRD MDVN-positive.

Assuming two-thirds of HRRD FMI-positive patients will be HRRD MDVN-positive, the total number of patients accrued to **S1400G** to achieve 40 eligible HRRD MDVN-positive patients is 60 eligible patients. Assuming that 5% of patients will be ineligible, the total accrual goal to the Phase II study is 64 HRRD FMI-positive patients.

The expected average monthly accrual rate is 2-3 patients per month with an anticipated duration of accrual of 28–30 months. Accrual and time estimates include a median 2-month time difference for patients screened at progression and median 9-month time difference for patients pre-screened prior to progression between screening and sub-study registration. Expected analysis times are stated from the date of sub-study activation.

Design and Analysis Plan within HRRD MDVN Positive Patient Population:
A Simon 2-stage minimax design with exact 93% power and 1-sided 0.07 level type I error would require 40 HRRD subset-positive patients to rule out an ORR of 15% or less if the true ORR is 35% or greater.

The analysis of Stage 1 ORR will take place when 20 HRRD subset positive patients are evaluable for response, with no halt in accrual. This interim analysis will only evaluate early stopping for futility. If 2 or fewer responses are observed, this will be considered evidence of futility and the recommendation will be to close the study (to all patients eligible for **S1400G**) for lack of evidence of efficacy of the regimen. If the study continues to stage 2 full accrual, the observation of at least 10 responses in the HRRD subset positive group will be considered evidence to rule out the null hypothesis of a 15% response rate if the true response rate is 35%.

Response rates and associated confidence intervals will be calculated. Survival and IA-PFS will be estimated using the method of Kaplan-Meier. The Brookmeyer-Crowley method will be used to calculate confidence intervals for median OS and IA-PFS. With 40 HRRD subset positive patients, ORR and toxicity rates can be estimated within 16% with 95% confidence. Any toxicity with at least 5% prevalence has at least an 87% chance of being observed.

A key secondary objective is an assessment of median IA-PFS (mPFS). If the observed 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 HRRD subset positive patients, this design has 90% power to rule out a median PFS 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 30 months of accrual and 6 months follow-up.

The observation of an mPFS of at least 4.5 months would be considered evidence to rule out an mPFS of 3 months or less.

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Analysis Plan and Properties for HRRD FMI-Positive Patients:
Secondary analyses will evaluate all patients (HRRD positive by FMI criteria) registered to **S1400G**. Response rates and associated confidence intervals will be calculated. Survival and IA-PFS will be estimated using the method of Kaplan-Meier. The Brookmeyer-Crowley method will be used to calculate confidence intervals for median OS and IA-PFS.

With 60 eligible patients registered to **S1400G**, ORR and toxicity rates can be estimated within 13% with 95% confidence. Any toxicity with at least 5% prevalence has at least a 95% chance of being observed.

Analysis Plan and Properties for HRRD MDVN-Negative/FMI-Positive Patients:
Additional secondary analyses will be to evaluate HRRD MDVN-negative/FMI-positive patients registered to **S1400G**. Response rates and associated confidence intervals will be calculated. With approximately 20 HRRD MDVN-negative/FMI-positive patients, the ORR can be estimated within 22% with 95% confidence.

Translational Medicine Analyses:
All HRRD FMI-positive patients with a biomarker value will be included in the relevant translational medicine analyses. A logistic regression model will be used to evaluate if Homologous Recombination Deficiency (HRD) IHC score (as both a continuous variable and categorized as high versus low) and PARP protein expression levels are associated with response. Current literature supports categorizing an HRD score greater than 10 as high, however should more data emerge on this categorization while the study accrues, the protocol and data analysis plan will be updated to account for this updated information. Similarly, a Cox regression model will be used to assess associations with PFS and OS.

12.0 DISCIPLINE REVIEW

This section does not apply to this sub-study.

13.0 REGISTRATION GUIDELINES

See Section 13.0 of **S1400** for registration guidelines.

13.1 Registration Timing

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

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 abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see section below for details.

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14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals 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 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 users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users 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.

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

b. 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.

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

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF **S1400G** REGISTRATION, SUBMIT:

S1400G Onstudy Form

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

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Radiology reports from all scans performed to assess disease at baseline (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 **S1400G** Section 15.5.

b. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0 of **S1400G**

c. WITHIN 7 DAYS AFTER EACH CYCLE (CYCLE = 21 DAYS) OF TREATMENT, SUBMIT:

S1400G Treatment Form

S1400G Adverse Event Form

S1400G Laboratory Values Form

For Cycle 1 only: submit the **S1400G** Pre-Treatment Laboratory Values Form and the **S1400G** Laboratory Values Form on Weeks 2 and 3 (in addition to the end-of-cycle Laboratory Values Form).

d. WITHIN 14 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION (see **S1400G** 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 **S1400G** Section 15.5.

e. WITHIN 7 DAYS OF DISCONTINUATION OF TREATMENT, SUBMIT:

Off Treatment Notice documenting reasons for off treatment

Smoking Status Assessment Form

S1400G Treatment Form

S1400G Adverse Event Form

S1400G Laboratory Values Form

f. ONCE OFF TREATMENT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1400G** REGISTRATION, THEN AT THE END OF YEAR 3 FROM SUB-STUDY REGISTRATION SUBMIT:

Advanced NSCLC Follow-Up Form

Late Effects Form (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] long term toxicity that has not been previously reported).

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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, in addition to follow-up on the new sub-study. (See Section 14.4i)

g. WITHIN 7 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 **S1400G** Section 15.5.

h. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information. In addition, if the patient was still on protocol treatment, submit materials specified in **S1400G** 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 7 DAYS OF PROGRESSION/RELAPSE:

Submit the **S1400** Request for New Sub-Study Assignment Form under **S1400** in Rave®. Continue follow-up on **S1400G** per Sections 9.0 and 14.4f. See Section 14.6 of **S1400** for additional data submission requirements following request for new sub-study assignment.

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

See **S1400** Section 5.1 for SWOG Specimen Tracking System (STS) instructions.

15.2 Correlative Studies and Banking (Optional for Patients)

Specimens for correlative studies 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. Peripheral Blood:

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 blood at pre-screening or screening (see Section 15.3 of **S1400**) and registration to the sub-study is within 42

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days from registration to **S1400**, then no additional pre-study blood specimen is required.
- Weeks 4, 7, 10
  Note: Patients that go off treatment are not required to continue to submit specimens.
- First progression (defined in Section 10 of **S1400G**) 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 labeled 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.

2. New Biopsy of Tumor at Time of Progression Among Responders (CR or PR) to talazoparib (BMN 673):

A new biopsy must be collected from patients who responded (CR or PR) to protocol treatment (in the opinion of the treating physician) and then experienced disease progression. Biopsies will be used for molecular analysis of molecular characteristics associated with mechanisms of resistance. New biopsy should be either bronchoscopy/surgical biopsy or CT guided biopsy.

Specimens should be collected at the following time point: within one month after progression.

Process the biopsy as FFPE material. The minimum requirement is a block or 12 unstained, charged, and unbaked 4-5 micron sections.

FFPE specimens (block or slides) should be shipped to the SWOG Biospecimen Bank at ambient temperature.

b. Specimen Submission

Samples for multiple patients can 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.

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Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources).

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

15.3 Talazoparib (BMN 673) Pharmacokinetic (PK) Analysis (Required)

Plasma specimens must be submitted for talazoparib (BMN 673) PK analysis from patients registered to **S1400G**.

Plasma samples will be shipped from each clinical site to Alliance Pharma (see Section 18.4 of **S1400G** for additional details).

a. Specimens must be submitted at the timepoints listed below. Collection and submission instructions are outlined in **S1400G** Section 15.3b.

One pre-dose and two postdose samples of peripheral blood will be collected at Day 1 of cycles 1-4. The predose sample must be collected within 30 minutes prior to dosing, the first postdose sample must be collected at least 30 minutes after dosing, and the second postdose sample must be collected at least 2 hours after the first postdose sample. The collection time of PK blood draws and drug administration must be recorded. All submitted specimens must be labeled with the treatment protocol number, SWOG patient number, patient initials, time point, and date of specimen collection, specimen number and/or specimen type.

Note: on days that PK sampling is scheduled, remind the patient to bring their tablets with them to the clinic and not to take that day's dose until instructed to do so. Patients who forget and take their dose may have PK sampling visit rescheduled, if possible.

b. **Specimen Collection and Submission Instructions**

- Collect approximately 5 mL of blood in K3 EDTA vacutainer; K2 EDTA tubes are not acceptable per protocol.
  - Please see **S1400G** Section 15.3c for instructions on ordering K3 tubes.
- Invert vacutainer gently 8-10 times.
- Centrifuge at 1500 x g for 10 minutes **at room temperature**. Each blood sample must be centrifuged within **1 hour** of draw.
- Evenly dispense the plasma between 2 cryovials. To avoid contamination, always use a new transfer pipette for each sample, and do not remove the plasma near the precipitate.
- Place the cryovials on dry ice until transfer to -70°C to -80°C freezer. Do not place cryovials on wet ice.
- Store at -70°C to -80°C until ready for shipment. Specimens must be shipped with sufficient dry ice to ensure they remain frozen upon arrival.
- Please ensure that information on the specimen tubes (e.g., collection time, collection date) matches the corresponding information listed on the SWOG Specimen Tracking System packing list.

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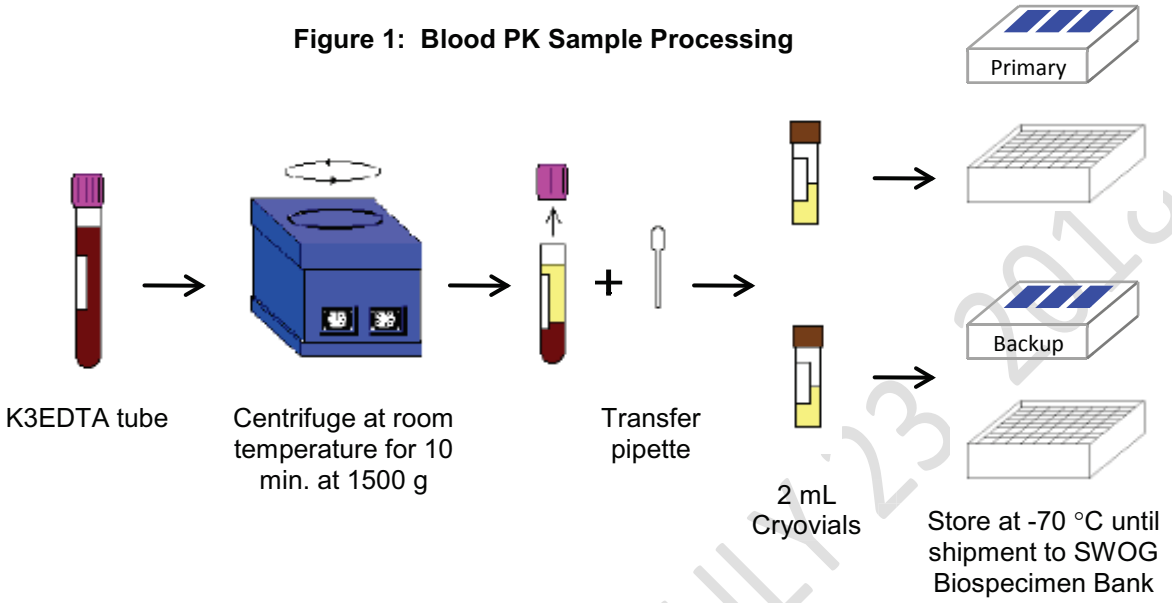
Figure 1: Blood PK Sample Processing



Samples for multiple patients can be shipped in batches, at least every 3 months if not more frequently, to Alliance Pharma, Lab #228 (see Section 18.4 of **S1400G** for additional details).

c. The K3 EDTA tubes for **S1400G** may be ordered from the SWOG Biospecimen Bank Kit Management system at: https://ricapps.nationwidechildrens.org/KitManagement/

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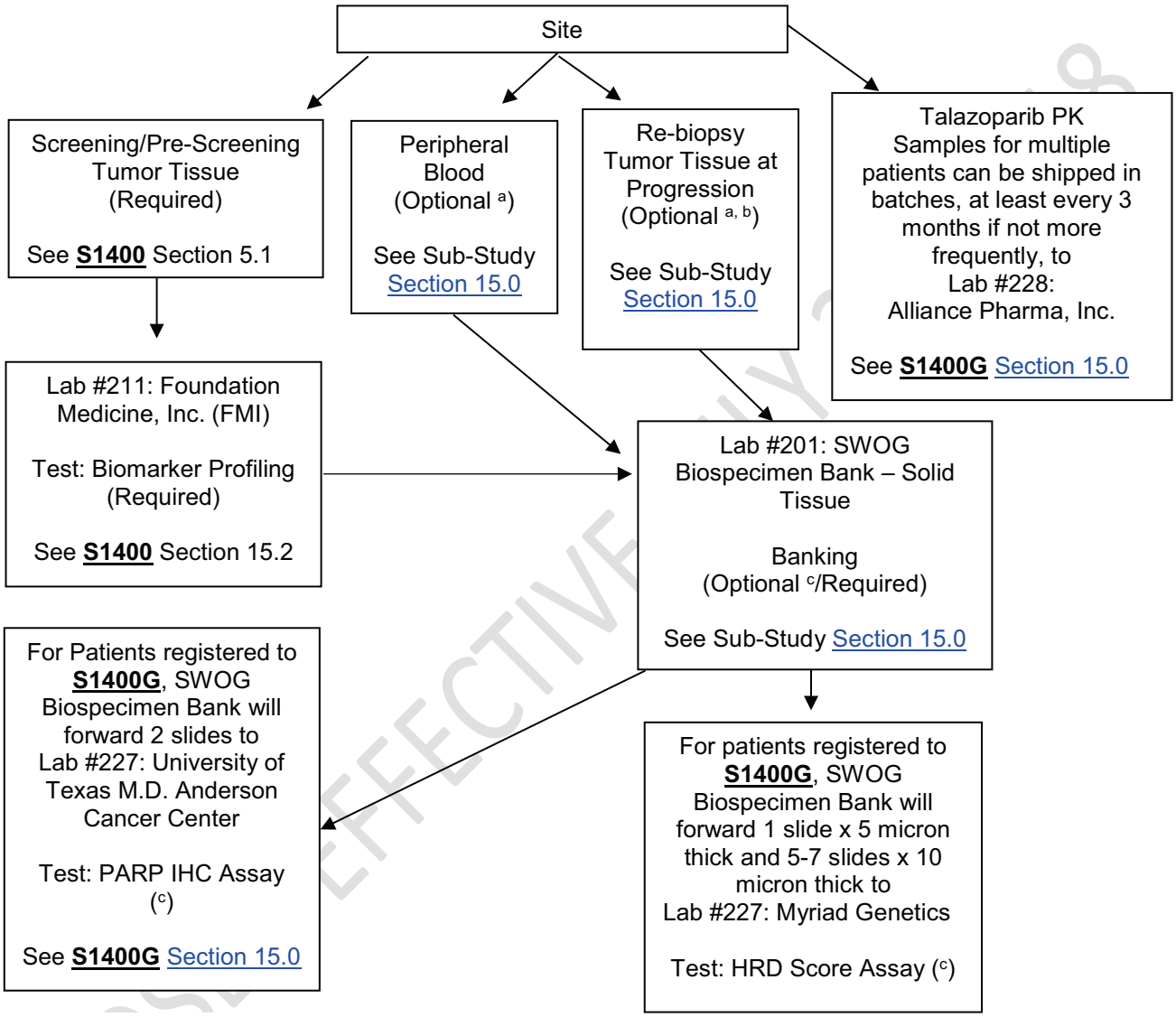
15.4 Specimen Flow Diagram



a With patient's consent.
b Among patients who initially responded to protocol treatment.
c 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. If the patient consented to future testing in **S1400**, 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 following timepoints:

- Baseline
- Every 6 weeks for the first year, then every 3 months until progression and treatment discontinuation

All study participants must have a CT (or MR or PET/CT) exam prior to sub-study entry. Participants must then undergo additional imaging every 6 weeks for the first year regardless of treatment delays, then every 3 months until disease progression and discontinuation of protocol treatment. The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see Section 10.1). Each exam should be performed per Section 18.1. 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 Section 18.1c of **S1400**.

b. TRIAD Digital Image Submission

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

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see **S1400** Section 13.2).

- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

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2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

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

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

15.6 HRD Score Assay and PARP IHC Assay Testing

Left over tissue from the screening NGS testing will be sent from the SWOG Biospecimen Bank to the appropriate laboratories for HRD Score Assay and PARP IHC Assay Testing (see Sections 18.1 and 18.2 for details). 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. If the patient consented to future testing in **S1400**, any leftover tissue will remain at the SWOG Biospecimen Bank for future exploratory analysis.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Adverse Event Reporting Requirements

a. Purpose

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 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. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

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. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

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When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1, as applicable.

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.

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 talazoparib (BMN 673). If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

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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/Intervention1 talazoparib (BMN 673), Arm 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 (if applicable) are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

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

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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 the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

a. Printed copy of the first page of the CTEP-AERS report
b. Copies of clinical source documentation of the event
c. If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center, copies of Off Treatment Notice and/or Notice of Death.

For this protocol, all second and secondary malignancies require expedited reporting via CTEP-AERS. Please refer to Section 16.1.g for further information.

2. The adverse events listed below also require expedited monitoring for this trial:

- ≥ Grade 2 AST or ALT if after evaluation it meets Hy's Law https://www.fda.gov/downloads/Drugs/.../guidances/UCM174090.pdf (See Sections IV.C, Case Report Forms and IV.E4, Assessment of Hy's Law Cases in the Clinical Trials Database)
- ≥ Grade 2 bilirubin

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.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.
For more information see:

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

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   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 Medivation

SWOG Operations will forward reports of all serious adverse events and events of overdose (defined as any dose above the protocol-specified dose of talazoparib [BMN 673]) **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.

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 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.*

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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

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18.1 Translational Medicine - HRD Score Assay

An HRD score assay will be performed on tumor specimens from patients registered to **S1400G**. Tumor specimens will be shipped from the SWOG Biospecimen Bank at Nationwide Children's Hospital to Myriad Genetics, Inc. at the conclusion of the study. The SWOG Statistics and Data Management Center will provide the SWOG Biospecimen Bank with the list of patient specimens to ship to Myriad.

Objective
To assess whether the HRD score associates with response to talazoparib (BMN 673) in squamous lung cancer patients.

Assay Description
HRD score is determined from a tissue based genomic assay that was developed in an attempt to facilitate the identification of patients likely to respond to platinum agents and PARP inhibitors. HRD score is a DNA-based assay based on whole genome tumor loss of heterozygosity (LOH) profiles (HRD-LOH score), telomeric allelic imbalance (HRD-TAI score), or large-scale state transitions (HRD-LST score). It provides a comprehensive signature for HRR deficiency. All three scores are highly correlated with defects in BRCA1/2 in breast or ovarian cancer and are associated with sensitivity to platinum agents.

Statistical Plan
A logistic regression model will be used to evaluate if HRD score (as both a continuous variable and categorized as high versus low) and PARP protein expression levels are associated with response. Similarly, a Cox regression model will be used to assess associations with PFS and OS.

Laboratory
Myriad Genetics will serve as the central laboratory for performing the HRD assay in patients who register to **S1400G**.

Lab #226
Myriad Genetics
Kirsten Timms
320 Wakara Way
Salt Lake City, UT 84108
801-584-3600
ktimms@myriad.com

Specimen Requirements
For HRD assay, no on-site processing of specimens will be required prior to shipment to the SWOG Biospecimen Bank. Tissue sample collected for **S1400** biomarker profiling will be used. For archival tissue slides, 1 slide x 5 micron thick section and 5–7 slides x 10 micron thick sections, with 20% tumor cellularity, are requested. For patients with tumor blocks at SWOG Biospecimen Bank, SWOG Biospecimen Bank will prepare the slides and ship to Myriad Genetics. The SWOG Biospecimen Bank will prepare 1 (5 micron thick) unstained, charged, and unbaked FFPE slide and 5-7 FFPE unstained, charged, and unbaked slides (10 micron thick).

For tissue samples submitted as slides, priority for remaining slides following the Foundation Medicine NGS testing will be given to the PARP IHC assay. Additional slides remaining following allocation for the PARP IHC assay will be used for the HRD score assay.

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18.2 PARP IHC Assay

PARP IHC testing will be performed on tumor specimens from patients registered to **S1400G**. Tumor specimens will be shipped from the SWOG Biospecimen Bank at Nationwide Children's Hospital to MD Anderson Translational Molecular Pathology lab at the conclusion of the study. The SWOG Statistics and Data Management Center will provide Nationwide with the list of patient specimens to ship to MD Anderson Translational Molecular Pathology lab.

Objective
To assess whether the level of PARP protein expression determined by immunohistochemistry is associated with response to talazoparib (BMN 673) in squamous lung cancer patients.

Assay Description
It is predicted that high PARP1 expression levels by IHC may be a biomarker of PARP inhibitor sensitivity in lung cancer. Patients with elevated PARP1 protein levels may demonstrate a superior outcome when treated with talazoparib (BMN 673) as second line or above treatment of squamous lung cancer.

Statistical Plan
A logistic regression model will be used to evaluate if HRD score (as both a continuous variable and categorized as high versus low) and PARP protein expression levels are associated with response. Similarly, a Cox regression model will be used to assess associations with PFS and OS.

Laboratory
MD Anderson Translational Molecular Pathology lab will serve as the central laboratory for performing the PARP IHC testing in patients who register to **S1400G**.

Lab #227
The University of Texas MD Anderson Cancer Center
Ignacio Wistuba, MD, in care of Jaime Rodriguez
Department of Translational Molecular Pathology - Unit 2951
2130 West Holcombe Boulevard, office LSP9.4029
Houston, TX 77030
713-563-9184
iiwistuba@mdanderson.org

Specimen Requirements
For PARP IHC testing, no on-site processing of specimens will be required prior to shipment to the SWOG Biospecimen Bank. The sample collected for **S1400** biomarker profiling will be used. For patients with tumor blocks at SWOG Biospecimen Bank, SWOG Biospecimen Bank will prepare two (4-5 micron) unstained, charged, and unbaked FFPE slides, plus an appropriate pathology image of one H&E slide per patient.

For tissue samples submitted as slides, priority for remaining slides following the Foundation Medicine NGS testing will be given to the PARP IHC assay. Additional slides remaining following allocation for the PARP IHC assay will be used for the HRD score assay.

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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 timepoints 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 2 timepoints 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.

Tumor Tissue for Immunotherapy Resistance Analysis
The SWOG Biospecimen Bank will send FFPE slides from consented patients for immunotherapy resistance analysis.

The Bank will send 5-10 unstained slides. If an FFPE tissue block was received, then the SWOG Biospecimen Bank will process up to 10 unstained slides (4 micron, charged, unbaked) to send for testing.

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18.4 Talazoparib (BMN 673) Pharmacokinetic (PK) Analysis

Objective
To characterize the pharmacokinetics (PK) of talazoparib (BMN 673) in patients with squamous cell lung cancer.

Assay Description
Limited sampling technique will be employed to characterize the PK of talazoparib (BMN 673) in this population. Plasma samples will be assayed for talazoparib (BMN 673) concentrations using a validated HPLC with MS/MS detection method, performed by Alliance Pharma, contract lab designated by Medivation Inc. Resulting concentration data will be summarized by visits and may be analyzed using a population PK modeling approach to provide, if supported by the data, population and individual estimates of talazoparib (BMN 673) PK parameters and exposure.

Statistical Plan
Descriptive statistics will be calculated for talazoparib (BMN 673) concentrations, and the estimated PK parameters. Statistics will include sample size (n), mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum.

Laboratory
Alliance Pharma, the contract lab designated by Medivation Inc. will serve as the central laboratory for performing the talazoparib (BMN 673) PK analysis in patients who register to **S1400G**.

Talazoparib (BMN 673) PK samples will be analyzed by Alliance Pharma Lab #228:

Yinghe Li, M.Sc.
Sr. Director
Bioanalysis
Alliance Pharma, Inc.
17 Lee Boulevard
Malvern, PA 19355
USA
Phone: 610-296-3152
Fax: 610-296-3153

Shipping address:
Attn: Sean Fairorth
Sample management
Alliance Pharma
17 Lee Blvd.
Malvern, PA19355
Ph: 610-296-3152
Email: sfairorth@alliancepharmaco.com

Specimen Requirements
For PK collection, sites will process specimens as outlined in Section 15.3 and will ship specimens to Alliance Pharma. Prior to shipping, samples are stored at -70ºC until ready for shipment.

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