PRIVILEGED COMMUNICATION
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S1900C: Talazoparib + Avelumab – *STK11*

SWOG CANCER RESEARCH NETWORK

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

S1900C, A PHASE II STUDY OF TALAZOPARIB PLUS AVELUMAB IN PATIENTS WITH STAGE IV OR RECURRENT NON-SQUAMOUS NON-SMALL CELL LUNG CANCER BEARING PATHOGENIC *STK11* GENOMIC ALTERATIONS (LUNG-MAP SUB-STUDY)

NCT#04173507

This is an FDA Registration Trial. Additional site requirements include:

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

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

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Talazoparib (PF-06944076) (NSC 771561)
Avelumab (NSC 799232)

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Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM):	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave or Delegation of Task Log (DTL):	See Protocol Section 14.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to Oncology Patient Enrollment Network (OPEN):	See **LUNGMAP** Protocol Section 13.2 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website(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 log in with a CTEP-IAM username and password.

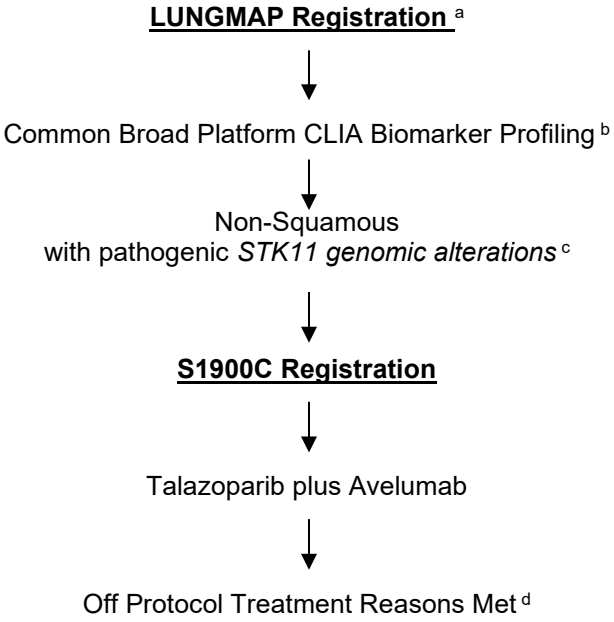
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email:

206/652-2267
LUNGMAPQuestion@crab.org

For treatment or toxicity related questions contact S1900CMedicalQuery@swog.org.

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

SCHEMA



a. See **LUNGMAP** Section 5.1 for registration information.

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

c. See **S1900C** Section 5.1 for the definition of eligible *STK11* genomic alterations by Foundation Medicine Inc. criteria.

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

1.0 OBJECTIVES

1.1 Primary Objectives

a. To evaluate the objective response rate (ORR) (confirmed and unconfirmed, complete and partial) with talazoparib plus avelumab in patients with Stage IV or recurrent non-squamous non-small cell lung cancer bearing pathogenic *STK11* genomic alterations that were previously-treated with anti-PD-1/PD-L1 therapy and platinum-based chemotherapy.

b. To evaluate disease control rate at 12 weeks (DCR12) after registration.

1.2 Secondary Objectives

a. To evaluate investigator assessed progression-free survival (IA-PFS).

b. To evaluate overall survival (OS).

c. To evaluate duration of response (DOR) among responders.

d. To evaluate the frequency and severity of toxicities.

1.3 Translational Medicine Objectives

a. To collect, process, and bank cell-free DNA (cfDNA) at baseline, Cycle 3 Day 1, progression, and end of treatment for future development of a proposal to evaluate comprehensive next-generation sequencing of circulating tumor DNA (ctDNA) and examine molecular mechanisms of resistance to talazoparib and avelumab.

Note: The translational medicine proposal to use these specimens will be submitted as a revision to CTEP for approval, prior to SDMC review of assay results.

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

c. To evaluate clinical outcomes (ORR, IA-PFS, OS) in patients with concurrent somatic mutations in *KEAP1* detected on the Foundation Medicine Inc. (FMI) panel from the **LUNGMAP** screening protocol.

d. To evaluate clinical outcomes (ORR, IA-PFS, OS) in patients with concurrent mutations in *ATM* or other DNA damage response genes detected on the FMI panel from the **LUNGMAP** screening protocol.

e. To evaluate the association between tumor mutational burden (TMB) measured on the FMI panel from the **LUNGMAP** screening protocol and clinical outcomes (ORR, IA-PFS, OS).

2.0 BACKGROUND

2.1 Rationale for Biomarker and Drug Selection

Inactivating genomic alterations in the *STK11* tumor suppressor gene represent one of the most common somatic genetic events in non-small cell lung cancer (NSCLC) (17% of all

lung adenocarcinomas-LUAC) and frequently co-occur with mutant *KRAS* (~25% of all *KRAS*-mutant NSCLC harbor *STK11* co-mutations). *(1,2)* *STK11* encodes *LKB1*, a serine threonine kinase with an established role in the regulation of cellular growth, metabolism and polarity through phosphorylation of AMP-activated protein kinase (AMPK) and 14 AMPK-related kinases (ARKs). *(3)* *STK11* somatic mutations are typically spread across the *STK11* gene without major hotspots, and are, in their vast majority, inactivating. *(4,5)*

Loss of function genomic alterations in *STK11* (non-synonymous mutations or bi-allelic loss) have been previously identified as a major determinant of primary resistance to PD-1/PD-L1 axis blockade in *KRAS*-mutant NSCLC and more broadly among non-squamous non-small cell lung cancer regardless of *KRAS* status. *(6,7,8, 9)* Loss of *STK11* is associated with establishment of a "cold", non-T-cell inflamed tumor immune microenvironment with low density of infiltrating CD8+ lymphocytes and low expression of PD-L1 on tumor cells. *(10,11,12,13)* Importantly, establishment of an inert tumor immune microenvironment in *STK11*-deficient NSCLC occurs despite the presence of intermediate or high tumor mutation burden. *(14,15,16)* It is also notable that the PD-1 inhibitor recalcitrant phenotype of *STK11* somatic genomic alterations extends to PD-L1 positive (PD-L1 tumor proportion score ≥1%) non-squamous non-small cell lung cancer, and is therefore at least partially independent of PD-L1 status. *(17)* In immune-competent murine models of non-small cell lung cancer (syngeneic as well as genetically engineered murine models) loss of *STK11* directly promotes PD-1 inhibitor resistance, supporting a causal effect. *(18,19)* Thus, *STK11*-deficient NSCLC represents a prevalent, molecularly-defined subgroup of NSCLC with *de novo* resistance to PD-1/PD-L1 inhibitor monotherapy, despite the presence of intermediate or high tumor mutation burden. More recently, *STK11* genomic alterations were also associated with worse clinical outcomes with pemetrexed/carboplatin (or cisplatin)/pembrolizumab. In addition, *STK11*-mutant patients harboring co-mutations in *KEAP1* exhibited lower ORR and shorter PFS and OS with chemo-immunotherapy. These findings support focused clinical efforts to identify rational combination therapeutic strategies aimed at re-establishing effective anti-tumor immunity in *STK11*-deficient tumors.

The rationale for combining PARP-inhibitors with PD-1/PD-L1 inhibitors

There is compelling rationale for combining PARP inhibitors with PD-1/PD-L1 inhibitors in order to enhance anti-tumor immune responses. Recent work in small cell lung cancer demonstrated that treatment with the PARP inhibitor olaparib can significantly potentiate the anti-tumor effect of PD-L1 blockade and trigger dramatic and sustained tumor regressions in immune competent animal models of small cell lung cancer. *(20)* Critically, the impressive clinical activity of combination therapy occurred despite the lack of significant anti-tumor activity of each individual agent, suggesting that sensitization to anti-PD-L1 therapy occurs as a result of the therapeutic combination. In agreement with this, combination therapy – but not each treatment alone - increased the densities of infiltrating CD3+ and CD8+ T lymphocytes. Notably, PARP inhibitor therapy resulted in increased tumor PD-L1 expression. *(21)*

Mechanistically, exposure to olaparib activates the STING/TBK1/IRF3 innate immune pathway that responds to cytosolic DNA. *(22, 23, 24)* Engagement of innate immune signaling leads to increased tumor cell expression of PD-L1 and production of *IFNβ* that promotes a type I interferon response. Importantly, activation of innate immune signaling results in the production of increased levels of CCL5 and CXCL10, chemokines that mediate the recruitment and activation of cytotoxic T lymphocytes. *(25)* Thus, engagement of innate immune signaling pathways mediates the profound synergy between olaparib and anti-PD-L1 therapy. In addition to promoting activation of the STING/TBK1/IRF3 pathway, DNA damage can further promote increased antigen presentation and increased expression of natural killer cell ligands (for example NKG2D), thus providing additional,

non-mutually exclusive pathways through which PARP inhibition may synergize with PD-1/PD-L1 blockade. *(26)*

Pre-clinical evidence of PARP inhibitor activity in *STK11*-mutant NSCLC

There is direct experimental evidence that *STK11*-deficient NSCLC cell lines are selectively sensitive to talazoparib and engage innate immune signaling following exposure to modest talazoparib concentrations. In order to assess the impact of *STK11* status on sensitivity to talazoparib in NSCLC, four previously established *STK11* proficient/deficient NSCLC pairs were utilized by re-introducing full-length functional *STK11* or empty vector in the H460, H2030, A549 and H23 *STK11*-mutant NSCLC lines that do not express *STK11* protein. *(27,28)* *STK11*-isogenic cell line pairs were then exposed to increasing concentrations of talazoparib *in vitro* for 72 hours. Strikingly, *STK11*-deficient derivatives of all four NSCLC lines (referred to as Control) were more sensitive to talazoparib compared with their *STK11* proficient counterparts (referred to as *LKB1* OE) that were resistant to talazoparib (Figure 1). These results suggest that in NSCLC cell lines, sensitivity to talazoparib is at least partially dependent on *STK11* status. Critically, exposure of the four *STK11*-deficient NSCLC cell lines (A549, H460, H2030 and H23) to low concentrations of talazoparib (50nM-100nM) for 48 hours resulted in elevated levels of phospho-TBK1 Ser172 protein, indicating that PARP inhibition engages innate immune signaling in this context (Figure 2). Thus, there is direct experimental evidence that exposure to talazoparib can result in immune pathway activation in *STK11*-deficient NSCLC cell lines. These results suggest that *STK11*-mutant NSCLC may be particularly amenable to combination therapy with talazoparib and avelumab. These results are further supported by work from other groups that showed that *STK11* deficiency is associated with sensitivity to different PARP inhibitors *(29)*, as well as to genetic and pharmacological inhibition of CHK1 *(30,31)* and pharmacological inhibition of the WEE1 kinase. *(32)* In addition, it was recently reported that *STK11* protein is recruited to sites of double-strand DNA breaks (marked by accumulation of γH2AX) upon genotoxic stress and plays a role in the regulation of BRCA1 expression through a post-transcriptional mechanism. *(33)* Thus, it has been postulated that *STK11* may exert a more direct role in the DNA damage response which may underpin the enhanced sensitivity of *STK11*-deficient NSCLC cell to PARP inhibitors.

Taken together these findings constitute rationale for combination therapy with PARP inhibitors and checkpoint inhibitor blockade to overcome the intrinsic resistance of *STK11*-mutant NSCLC to PD-1/PD-L1 inhibitor monotherapy.

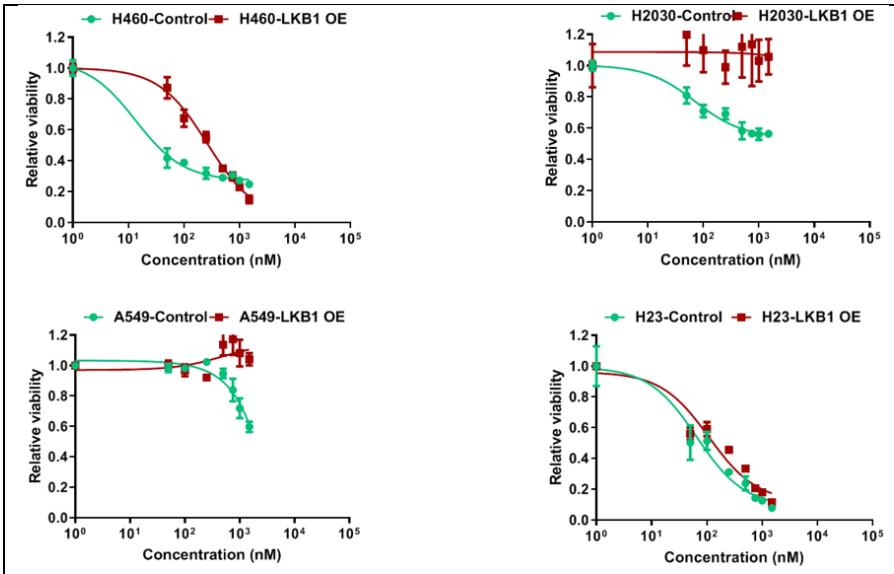


Figure 1. Sensitivity of NSCLC cell lines to talazoparib is at least partially dependent on *STK11* status. Dose response curves of four *STK11* deficient /proficient isogenic non-small cell lung cancer cell line pairs to the PARP1 inhibitor talazoparib. Cell viability was measured after exposure to the indicated concentrations of talazoparib for 120 hours using the Cell Counting Kit-8 (Dojindo Molecular Technologies, Inc). **Note that in each of the four isogenic pairs *STK11* deficiency is associated with increased sensitivity to talazoparib, whereas re-introduction of full-length *STK11* confers resistance.**

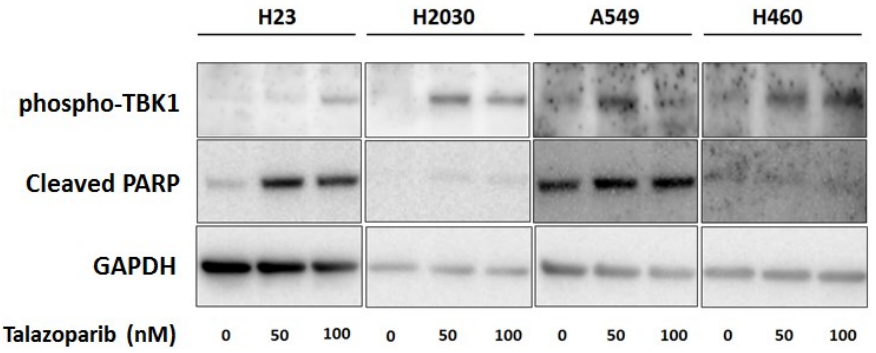


Figure 2. Engagement of innate immune signaling following exposure to talazoparib in *STK11*-mutant NSCLC cell lines. Immunoblotting for phospho-TBK1 (Ser172), a marker of innate immune pathway activation following exposure to the indicated concentrations of talazoparib for 72 hours in four naturally *STK11*-deficient non-small cell lung cancer cell lines. Cleaved PARP is a marker of apoptosis and GAPDH serves as loading control. Note that exposure to modest concentrations of talazoparib results in increased expression of phospho-TBK1 in all four *STK11* deficient NSCLC cell lines. These results indicate that treatment with talazoparib results in activation of innate immune signaling in *STK11*-deficient NSCLC cell lines.

2.2 Rationale for Inclusion in Lung-MAP

The Lung-MAP study is a master protocol for genomic screening and multi-sub-study testing of drug/biomarker combinations in a Phase II/III setting compatible with subsequent FDA approval. Genomic screening of a large patient resource provided by sites participating in the NCI National Clinical Trials Network (NCTN) identifies a series of molecular targets/biomarkers which are matched to new drugs, leading to appropriate sub-study assignment and drug treatment. Each molecular target in Lung-MAP is represented by a biomarker for which there is an analytically validated diagnostic assay. This approach

provides the basis for this large-scale screening/clinical registration trial with the ability to screen patients, either through genomic analysis or immunohistochemistry-based assays, with homogeneous eligibility criteria and direct them to a sub-study based on the results of screening diagnostic tests.

Based on the results of the tumor analysis, patients will either be assigned to one of the biomarker-driven sub-studies or to a 'non-match' sub-study for patients with none of the eligibility biomarkers. The biomarker-driven sub-studies are designed around a genotypically-defined alteration in the tumor and a drug that targets it. The non-match studies are designed around an investigational agent with the potential for efficacy in a broader population. For a full description and justification of the study design, refer to the **LUNGMAP** Screening Protocol.

Prevalence of *STK11* somatic mutations and bi-allelic loss in non-squamous non-small cell lung cancer:

Based on data from the TCGA as well as the Foundation Medicine database, the frequency of pathogenic somatic mutations and bi-allelic deletions in *STK11* is ~17% of non-squamous NSCLC. In view of the low prevalence of *STK11* genomic alterations in pure squamous cell lung cancer and the lack of preliminary data regarding the impact of *STK11* genomic alterations on clinical outcomes with PD-1 axis blockade in this histological subtype, patients with pure squamous non-small cell lung cancer will not be included in this study.

2.3 Study Design

This is a single arm, open label signal seeking study assessing the efficacy of talazoparib plus avelumab in patients with non-squamous NSCLC with pathogenic *STK11* genomic alterations (mutations or bi-allelic deletion using the FoundationOne assay), whose disease has progressed following initiation of platinum-doublet chemotherapy and anti-PD-1 or anti-PD-L1 therapy, administered concurrently or sequentially. The co-primary objectives are to evaluate the response rate and disease control rate at 12 weeks for talazoparib and avelumab among patients found to have pathogenic *STK11* genomic alterations on tumor genomic profiling using the FoundationOne assay.

2.4 Rationale

Inactivating *STK11* genomic alterations are prevalent in non-squamous NSCLC (~17%) and constitute a major driver of primary resistance to PD-1 axis blockade, irrespective of tumor cell PD-L1 expression and tumor mutational burden. Given the high prevalence of *STK11* alterations in non-squamous NSCLC, identification of rational therapeutic approaches to restore effective anti-tumor immunity in this molecular subset constitutes a major unmet clinical need. Combination of talazoparib, a potent catalytic PARP inhibitor with additional PARP trapping activity with avelumab, a fully human PD-L1 inhibitory antibody, represents a rational therapeutic strategy for this immunotherapy resistant subgroup of NSCLC. If successful, this approach has the potential to result in meaningful prolongation of overall survival and improved quality of life for non-squamous NSCLC patients bearing *STK11* mutant tumors.

2.5 Data

Avelumab (10mg/kgr IV every 2 weeks) was compared with docetaxel for patients with Stage IIIB, IV or recurrent NSCLC and disease progression after treatment with a platinum-containing doublet in the randomized open label JAVELIN Lung 200 Phase 3 clinical trial. *(34)* Among 529 PD-L1 positive patients (≥1% cutoff) the ORR with avelumab was 19% compared to 12% in the docetaxel group (OR 1.76, 95% CI 1.08-2.86; P=0.011). Overall

survival did not differ significantly between the two groups (mOS 11.4 months [95% CI 9.4-13.9] vs 10.3 months [8.5-13.0]; HR 0.90 [96% CI 0.72-1.12]; one sided P=0.16). Avelumab was overall well tolerated with grade 3-5 adverse events observed in 10% of avelumab-treated patients. In the avelumab group, the most common treatment-related adverse events (All grade) were infusion-related reactions (17%) and decreased appetite (9%) and the most common grade 3 or worse treatment-related adverse events were infusion-related reaction (2%) and increased lipase (1%).

Talazoparib was evaluated in the first-in-human multicenter Phase I study NCT01286897 consisting of a dose-escalation (Part 1) cohort in patients with solid tumors and a dose expansion (Part 2) cohort in patients with tumors predicted to be potentially sensitive to PARP inhibition, including patients with germline pathogenic BRCA1/2 mutations; triple-negative breast cancer; high grade serous papillary and/or undifferentiated ovarian, fallopian tube or peritoneal cancers; castration-resistant prostate and pancreatic cancers, Ewing's sarcoma and small cell lung cancer. *(35)* The MTD and RP2D was determined to be 1 mg/day, with an elimination half-life of 50 hours. The most common G3/G4 treatment-related adverse events were anemia (24%), thrombocytopenia (18%) and neutropenia (10%). Among 23 patients with small cell lung cancer enrolled in the dose expansion cohort and treated with 1 mg/day of talazoparib the ORR was 9% and the clinical benefit rate (defined as PR/CR + SD lasting ≥16 weeks) was 26%.

The combination of avelumab plus talazoparib is being evaluated in the open-label phase 1b/2 JAVELIN PARP Medley (B9991025, NCT03330405) clinical trial in ~316 PD-1/PD-L1 inhibitor- naïve patients with selected solid tumors, including patients with NSCLC. Different daily doses of talazoparib plus avelumab at a fixed dose of 800mg IV Q2W are administered during the Phase 1b to define the RP2D for the combination. As of May 18, 2018 among 12 patients enrolled at dose level D0 (talazoparib 1.0mg PO QD, avelumab 800mg IV Q2W) in 3 sequential cohorts (n=9 CRPC; n=2 TNBC, n=1 ovarian cancer) that completed the DLT monitoring period and were evaluable for DLT only 1 SAE of anemia was reported, with no G3 AEs other than hematologic toxicities and no Grade 4-5 AEs. Therefore, the RP2D for the talazoparib/avelumab combination was talazoparib 1 mg PO QD days 1-28 and avelumab 800mg IV Q2W. Phase 2 enrollment opened on June 01, 2018 and is ongoing (communication with Pfizer).

2.6 Inclusion of Women and Minorities and Planned Enrollment Report

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

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	2	0	0	3
White	17	21	1	1	40
More Than One Race	0	0	0	0	0
Total	18	24	1	1	44

3.0 DRUG INFORMATION

Investigator Brochures

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

For this sub-study, talazoparib and avelumab are investigational and are 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's Brochure from the company, requests may be submitted to the CTSU website by completing the CTSU Request for Clinical Brochure.

3.1 Talazoparib (PF-06944076) (NSC 771561) (IND143217)

a. PHARMACOLOGY

Mechanism of Action: Talazoparib is a highly potent and specific inhibitor of PARP1 and 2 with activity in tumor cell lines bearing DNA repair deficiencies. Treatment with a PARP inhibitor results in cell cycle arrest and apoptosis.

b. PHARMACOKINETICS

1. Absorption: Absorption of talazoparib 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 hours. Food delays absorption of talazoparib but has no effect on the extent of absorption.

2. Distribution: Protein binding of talazoparib 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 accumulated approximately 2.4-fold relative to a single dose.

3. Metabolism: Overall, talazoparib 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. 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 Events 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 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 (MDV3800, BMN 673).

Version 2.4, October 24, 2020[1]

Adverse Events with Possible Relationship to Talazoparib (MDV3800, 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		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
	Pain	
INFECTIONS AND INFESTATIONS		
	Infection[2]	
INVESTIGATIONS		
	Lymphocyte count decreased	
Neutrophil count decreased		

Adverse Events with Possible Relationship to Talazoparib (MDV3800, BMN 673) (CTCAE 5.0 Term) [n= 553]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
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
		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 (MDV3800, BMN 673) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that talazoparib (MDV3800, 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 (metastases to meninges); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastatic breast cancer)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Intracranial hemorrhage; Nervous system disorders - Other (neuropathy peripheral)[3]; Nervous 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 (MDV3800, 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 on pregnancy have not been performed. Women of childbearing potential should use highly effective contraceptive measures during and for at least 7 months after completion of treatment. Non-sterilized males who are sexually active with a female partner should use highly effective contraceptive measures during and for at least 4 months after completion of treatment. Male patients must not make sperm donations during treatment and for 4 months following the last dose of treatment.

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

3. Drug Interactions:

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

Talazoparib is a substrate for P-gp and BCRP, and plasma talazoparib concentrations may increase or decrease when co-administered with P-gp or BCRP inhibitors or inducers, respectively. Guidelines for concomitant use of talazoparib 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, oral 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).

Please note that this list is not all-inclusive. Because lists of these agents are constantly changing, it is important to regularly consult a frequently updated list for the most up-to-date listing of agents; medical reference texts such as the Physicians' Desk Reference may also provide this information.
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

1. Talazoparib is supplied by Pfizer and distributed by Pharmaceutical Management Branch (PMB).

Talazoparib is a capsule formulation comprised of a blend of talazoparib 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 at room temperature (15-30 ºC; 59-86 ºF). Contact Pfizer for temperature excursion information.

If a storage temperature excursion is identified, do not use the affected investigational product. The investigational product must be stored separately in an appropriate location pending the final disposition decision. Return the investigational product that underwent the temperature excursion in the appropriate storage conditions and quarantine until a suitable determination is made. In case of temperature excursion at the

site outside of storage range, complete the Site Temperature Excursion Report Form (see Appendix 18.6) and email to GCSTempExcursionSupport@pfizer.com. In the email correspondence, reference the Pfizer tracking number for this study: WI247821.

Talazoparib 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 the patient and caregivers should always use gloves when handling capsules. For additional patient instructions, see Section 7.4.

3.2 Avelumab (MSB0010718C; Bavencio®) (NSC 799232) (IND 143217)

a. PHARMACOLOGY

Mechanism of Action: Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on antitumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

b. PHARMACOKINETICS

Absorption: Avelumab is administered intravenously and is 100% bioavailable.

Distribution: Avelumab is expected to be distributed in the systemic circulation and to a lesser extent into the extracellular space. In vitro studies suggest that avelumab binds to human tissues that are known for PD-L1 expression: various epithelial cell types, endothelium, mononuclear cells (including dendritic cells, lymphocytes, monocytes and macrophages), pancreatic islets, placental trophoblasts and decidual cells, smooth muscle cells, and mesenchymal stem cells. The volume of central and peripheral compartments is estimated to be 2.84L and 1.21L in the typical patient, respectively. The geometric mean V_{ss} for a patient receiving 10mg/kg was 4.72L, which is consistent with distribution mainly limited to systemic circulation.

Metabolism: Avelumab is degraded by proteolytic catabolism. CYP450 does not contribute to its metabolism.

Elimination: The primary route of elimination of avelumab is through proteolytic degradation. The geometric mean clearance calculated by noncompartmental analyses [Study EMR100070-001] was estimated as 0.362mL/hr/kg for an initial 10mg/kg/dose. The corresponding value for Japanese patients [Study EMR100070-002] was calculated as 0.471mL/hr/kg at the 10mg/kg dose. The estimate of clearance obtained for a typical patient in population pharmacokinetic analysis was 0.0246 L/hr. Population pharmacokinetic analysis and noncompartmental analysis results are comparable.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events 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 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 1738 patients. Below is the CAEPR for Avelumab.

Version 2.0, April 23, 2019[1]

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n=1738]		
Likely (> 20%)	**Less Likely (4 - ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
		Adrenal insufficiency[2]
		Hyperthyroidism[2]
		Hypophysitis[2]
		Hypopituitarism[2]
	Hypothyroidism[2]	
EYE DISORDERS		
		Uveitis[2]
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
		Colitis[2]
	Diarrhea	
	Nausea	
	Pancreatitis[2]	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
	Fever	
	Flu like symptoms[3]	
HEPATOBILIARY DISORDERS		
		Hepatic failure[2]
		Hepatobiliary disorders - Other (autoimmune hepatitis, immune-related hepatitis)[2]
IMMUNE SYSTEM DISORDERS		
		Autoimmune disorder[2]
		Cytokine release syndrome[3]
		Immune system disorders - Other (sarcoidosis)[2]
INFECTIONS AND INFESTATIONS		
	Infection[4]	

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n=1738]		
Likely (> 20%)	**Less Likely (4 - ≤ 20%)**	**Rare but Serious (≤ 3%)**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction[3]	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	CPK increased	
	Creatinine increased	
	GGT increased	
	Lipase increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Platelet count decreased	
	Serum amylase increased	
	Thyroid stimulating hormone increased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Hyperglycemia[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	
	Generalized muscle weakness	
	Muscle cramp	
	Myalgia[2]	
		Myositis[2]
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
		Encephalopathy[2]
		Guillian-Barre syndrome[2]
		Myasthenia gravis[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]
		Peripheral motor neuropathy
		Peripheral sensory neuropathy[2]

Adverse Events with Possible Relationship to Avelumab (CTCAE 5.0 Term) [n=1738]		
Likely (> 20%)	**Less Likely (4 - ≤ 20%)**	**Rare but Serious (≤ 3%)**
RENAL AND URINARY DISORDERS		
		Renal and urinary disorders - Other (immune related nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
		Pneumonitis[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Eczema	
	Pruritus	
	Rash acneiform	
	Rash maculo-papular	

[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]Immune-mediated adverse reactions have been reported in patients receiving avelumab. Adverse events potentially related to avelumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of avelumab), administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of avelumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of avelumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

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

CARDIAC DISORDERS - Palpitations; Sinus tachycardia
EYE DISORDERS - Blurred vision; Dry eye
GASTROINTESTINAL DISORDERS - Abdominal distension; Constipation; Dry mouth; Dyspepsia; Flatulence; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Electrocardiogram QT corrected interval prolonged; Investigations - Other (c-reactive protein increased); Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare); Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysgeusia; Headache; Tremor
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension

Note: Avelumab 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: Based on its mechanism of action, avelumab can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with avelumab and for at least one month after the last dose of avelumab. There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise lactating women not to breastfeed during treatment and for at least one month after the last dose of avelumab due to the potential for serious adverse reactions in breastfed infants.

3. Special Populations: No dedicated clinical studies have been conducted to evaluate the effect of renal or hepatic impairment on the pharmacokinetics of avelumab. Even though a limited number of patients with severe renal impairment have been studies, renal impairment is not expected to have an effect on the pharmacokinetics of avelumab. here are limited data from patients with severe hepatic impairment, and the effect of severe hepatic impairment on the pharmacokinetics of avelumab is not known.

4. Drug Interactions: No interaction studies have been conducted with avelumab in humans.

d. DOSING & ADMINISTRATION
See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Avelumab is supplied by Merck KGaA/EMD Serono, Inc./Pfizer and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 200 mg vials containing a sterile solution of 10 mL total volume (20 mg/ml). Avelumab is a clear and colorless to slightly yellow concentrate for solution containing D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, and water for injection, and supplied in glass vials closed with a rubber (not made with natural

rubber latex) stopper and sealed with an aluminum crimp seal closure fitted with a removable plastic cap.

f. STORAGE, PREPARATION & STABILITY

1. Avelumab must be stored under refrigeration (2°-8° C, 36-46º F) and protected from light until use. Avelumab must not be frozen. Rough shaking must be avoided during handling and preparation.

2. Prepare avelumab solution under a laminar flow hood using aseptic technique. If a laminar flow hood is not available, alternative procedures and aseptic handling techniques that prevent microbiological contamination may be used.

3. Prior to preparation of the dilution for infusion, allow vial(s) to equilibrate to room temperature. The measured dose should be diluted with 250 mL 0.9% Sodium Chloride or 0.45% Sodium Chloride solution. Gently invert the mixture 10 times. Do not shake infusion bag in order to avoid foaming and/or excessive shearing of the protein solution. Carefully inspect the prepared dose to confirm homogeneity of the solution and that it is free of any visible particles or discoloration.

4. Prepared solutions of avelumab should be used immediately. If not used immediately, diluted avelumab may be stored for up to 4 hours at room temperature (15°C-25°C) or up to 24 hours under refrigeration (2°C to 8°C); this includes infusion time. Note that the time interval for stability begins at the time the intact avelumab vials are removed from the refrigerator and allowed to reach room temperature for dose preparation. If finished doses are stored under refrigeration, allow the bag containing avelumab to come to room temperature.
If a storage temperature excursion is identified, do not use the affected investigational product. The investigational product must be stored separately in an appropriate location pending the final disposition decision. In case of temperature excursion at the site outside of storage range, complete the Site Temperature Excursion Report Form (see Appendix 18.6) and email to GCSTempExcursionSupport@pfizer.com. In the email correspondence, reference the Pfizer tracking number for this study: WI247821.

5. No other drugs should be added to the solution of avelumab for infusion.

6. Administer diluted avelumab solution through infusion tubing with a sterile, non-pyrogenic, low protein binding, 0.2-micron in-line filter. Do not co-administer other drugs through the same IV line.

3.3 NCI-Supplied Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP assigned protocol number (**S1900C**) must be used for ordering all CTEP supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

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

No starter supplies may be ordered. Patients must be enrolled and registered to protocol **S1900C** prior to order submission through OAOP.

Useful Links and Contacts

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

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

a. Drug Return and/or Disposition Instruction

1. Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

2. 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 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.

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.

4.0 STAGING CRITERIA

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

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

Primary Tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 No evidence of primary tumor
Tis Carcinoma in situ
Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤ 3 cm in greatest dimension
T1 Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension
T1a Tumor ≤ 1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b Tumor > 1 cm but ≤ 2 cm in greatest dimension
T1c Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2 Tumor > 3 cm but ≤ 5 cm or having any of the following features:
- Involves the main bronchus regardless of distance to the carina, but without involvement of the carina
- Invades visceral pleura (PL1 or PL2)
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung

T2 tumors with these features are classified as T2a if ≤ 4 cm or if the size cannot be determined and T2b if > 4 cm but ≤ 5 cm.
T2a Tumor > 3 cm but ≤ 4 cm in greatest dimension
T2b Tumor >4 cm but ≤ 5 cm in greatest dimension
T3 Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium, or separate tumor nodule(s) in the same lobe as the primary
T4 Tumor > 7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

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

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration in OPEN. Section 5 may be printed and used to by the site, but is not to be uploaded in RAVE (unless specially stated). 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 (SDMC) in Seattle at 206/652-2267 or LUNGMAPQuestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion** (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

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

5.1 Disease Related Criteria

a. Patients must be assigned to **S1900C**. Assignment to **S1900C** is determined by the **LUNGMAP** protocol genomic profiling using the FoundationOne assay. Biomarker eligibility for **S1900C** is based on the identification of a pathogenic somatic mutation in *STK11* or *STK11* bi-allelic loss on tumor.

b. Patients must have histologically or cytologically confirmed Stage IV or recurrent non-squamous, mixed squamous/non-squamous (e.g., adeno-squamous carcinoma), or non-small cell lung cancer not otherwise specified (NSCLC NOS). Patients with pure squamous cell carcinoma are not eligible.

c. Patients with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load on suppressive therapy within 28 days prior to sub-study registration.

d. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with HCV infection who are currently on treatment must have an undetectable HCV viral load within 28 days prior to sub-study registration.

e. Patients with known human immunodeficiency virus (HIV) infection are eligible, provided they are on effective anti-retroviral therapy and have undetectable viral load at their most recent viral load test and within 6 months prior to sub-study registration.

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

5.2 Prior/Concurrent Therapy Criteria

a. Patients must have received at least one line of anti-PD-1 or anti-PD-L1 therapy for Stage III, IV or recurrent disease.

Any number of additional, non-platinum-based chemotherapy or targeted therapy regimens for recurrent or metastatic disease are allowed.

1. Patients may not have received more than one line of anti-PD-1 or anti-PD-L1 therapy in the Stage IV or recurrent setting. Anti-PD-1 or anti-PD-L1 therapy may have been given alone or in combination with platinum-based chemotherapy, an anti-CTLA4 therapy, or other immune-modulatory therapy. Patients must have experienced disease progression>42 days following initiation (Cycle 1 Day 1) of the anti-PD-1 or anti-PD-L1 containing regimen.

2. Patients, must have received prior platinum-based chemotherapy and experienced disease progression >42 days following initiation (Cycle 1 Day 1) of platinum based chemotherapy. Note: Patients may have received this in combination with anti-PD-1 or anti-PD-L1.

3. Patients who received anti-PD-1 or anti-PD-L1 therapy following concurrent chemoradiation for Stage III disease as their only line of anti-PD-1 or anti-PD-L1 therapy, are eligible if they experienced disease progression less than (<) 365 days from the date of initiation of anti-PD-1 or anti-PD-L1 therapy.

b. Patients who received prior adjuvant platinum-based therapy post-surgical resection for Stage I-III disease (i.e. the patient has not received platinum-based chemotherapy for Stage IV or recurrent disease) must have had disease progression during or after platinum-based chemotherapy that occurred less than (<) 365 days from the last date that the patient received that therapy.

c. Patients must be able to swallow capsules whole.

d. Patients must not have had prior exposure to any agent with a PARP inhibitor (e.g., veliparib, olaparib, rucaparib, niraparib, talazoparib) as its primary pharmacology.

e. Patients must not be taking, nor plan to take while on protocol treatment strong P-gp inhibitors, P-gp inducers, or strong breast cancer resistance protein (BCRP) inhibitors. Please refer section 3.1 c. for detailed information.

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

g. Patients must not have received prior systemic immunotherapy within 28 days prior to sub-study registration and must not have received any prior systemic therapy (including systemic chemotherapy 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 5.3b for criteria regarding therapy for CNS metastases).

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

5.3 Clinical/Laboratory Criteria

a. Patients must have measurable disease (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 sub-study registration. See Sections 15.5 and Appendix 18.2 for guidelines and submission instructions for required central radiology review. CT and MRI scans must be submitted for central review via TRIAD.

b. 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 sub-study registration, AND (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

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

d. 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).

e. Patients must have a serum creatinine ≤ the IULN or calculated creatinine clearance ≥ 60 mL/min using the following Cockroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to sub-study registration:

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

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 0.7 mg/ dL.

Creatinine Calculator:
https://crawb.crab.org/TXWB/CreatinineClearanceCalculator.aspx

f. Patients' most recent Zubrod performance status must be 0-1 (Section 10.4) documented within 28 days prior to sub-study registration.

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

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

i. 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.

j. 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.

k. Patients must not have a history of prior organ transplantation, including allogeneic stem-cell transplantation.

l. Patients must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days prior to sub-study registration. Inhaled or topical steroids, and adrenal replacement doses ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

m. Patients must not have active autoimmune disease that requires systemic steroids (equivalent of >10 mg of prednisone) or immunosuppressive agents within 14 days prior to sub-study registration (for example disease-modifying anti-rheumatic drugs). Exceptions include: patients with controlled type 1 diabetes mellitus, controlled hypo- or hyperthyroidism, vitiligo, resolved childhood asthma/atopy, or psoriasis not requiring immunosuppressive therapy.

n. Patients must not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of talazoparib (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or active peptic ulcer disease). Note: peptic ulcer is considered non-active if clinically stable for 1 month.

o. Patients must not have active small or large intestine inflammation such as Crohn's disease or ulcerative colitis within 12 months prior to sub-study registration.

p. Patients must not have known prior or suspected hypersensitivity to monoclonal antibodies (Grade ≥3).

q. Patients must not have any history of anaphylaxis or uncontrolled asthma.

Uncontrolled asthma is defined as a patient having any one of the following criteria:

1. Poor symptom control: ACQ consistently >1.5 or ACT <20 (or "not well controlled" by NAEPP or GINA guidelines over the 3 months or evaluation).

2. Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year.

3. Serious exacerbations: at least one hospitalization, Intensive Care Unit stay or mechanical ventilation in the previous year.

4. Airflow limitation: FEV1<80% predicted (in the presence of reduced FEV1/FVC defined as less than the normal lower limit) following a withhold of both short- and long-acting bronchodilators.

r. Patients must not have experienced any immune related adverse event (including but not limited to pneumonitis), that led to permanent discontinuation of prior immunotherapy and/or required prolonged high dose of steroids (defined as>10mg daily prednisone or equivalent for more than 56 days (8 weeks)).

s. Patients must not have evidence of active infection requiring systemic therapy.

t. Patients must not have received any live attenuated vaccinations within 28 days prior to sub-study registration.

u. 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. Patients must be transfusion independent (i.e., no blood product transfusions for a period of at least 14 days prior to sub-study registration).

5.4 Specimen Submission Criteria

a. Patients must agree to have blood specimens submitted for circulating tumor DNA (ctDNA) as outlined in Section 15.3.

b. Patients must also be offered participation in banking and in the correlative studies for collection and future use of specimens as described in Section 15.4.

5.5 Regulatory Criteria

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

b. As a part of the OPEN registration process (**LUNGMAP** Section 13.2 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

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

investigator). For patients with impaired decision making capabilities, legally authorized representatives may sign and give informed consent on behalf of study patient in accordance with applicable federal, local, and CIRB regulations.

6.0 STRATIFICATION FACTORS

There are no stratification factors in this study.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Ferdinandos Skoulidis and Dr. Jennifer Marie Suga at S1900CMedicalQuery@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 Precautions

See Section 3.0 and Appendix 18.5 for drug interactions and precautions.

Patients must not receive any live attenuated vaccinations during protocol treatment.

7.2 Pre-Medication and Supportive Care

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

b. In order to mitigate infusion-related reactions, a premedication with an antihistamine and with acetaminophen 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg acetaminophen IV or oral). Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.

c. Small volume, low dose palliative radiotherapy (≤ 20 Gy) for painful bone metastases is permitted, provided that no target lesions are encompassed, and the patient does not have progression as defined in Section 10.0. Delaying the next dose of protocol therapy by up to two weeks is permitted.

7.3 Disease Assessment

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

Disease Assessment During Treatment
CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.3) must be performed on week 6 (± 7 day window), week 12 (± 7 day window), and then every 8 weeks (± 7 day window) thereafter regardless of treatment delays, until discontinuation of protocol treatment. The 6 weeks should start from sub-study registration. If the patient remains on protocol treatment after progression due to clinical benefit in the opinion of the treating investigator (per Section 7.6), scans must continue per protocol schedule until treatment is discontinued.

Pre-study Brain CT/MRI is required per Section 5.3. If patient has brain metastases at baseline, scans must use the same modality as baseline and be repeated at week 12 (± 7 days) and every 8 weeks (± 7 days) thereafter while on treatment.

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

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

7.4 Treatment – **S1900C**

Agent	Dose	Route	Schedule *
Talazoparib	1000 mcg	PO	Daily
Avelumab	800 mg	IV over 60 mins	Days 1 & 15

* Note: One cycle = 28 calendar days

Setting: Avelumab should be administered in a setting that allows for access to and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids, epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Sites must have a plan to contact emergency services to provide prompt advanced life support including intubation.

Observation period: Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

Patient Instructions:
Patients should be advised that talazoparib is a toxic substance and that patients and their caregivers should always use gloves when handling capsules.

Patients should be instructed to swallow talazoparib capsules whole and not to chew them prior to swallowing. Talazoparib 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.

If more than 12 hours has elapsed from usual dose time (e.g. 10am), patient should consider that day skipped, and he/she should resume treatment the next day at the usual time.

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.

Note: On days the patient is in-clinic, there are no study dosing order of study drugs.

7.5 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Patient Diary (see Appendix 18.4). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. The Patient Diary should be kept in the patient's research chart. All sites ***must*** use the Patient Diary provided. CIRB requires that the provided Patient Diary be utilized for this study.

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Sections 10.2d and 10.2e). However, the patient may continue protocol treatment as long as the patient is continuing to clinically benefit from treatment in the opinion of the treating investigator. Patients should still be removed from protocol treatment for criteria below.

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

b. Unacceptable toxicity.

c. Treatment delay for any reason is > 28 days except for patients receiving steroid therapy for an immune related adverse event (as noted in Section 8.0). If patient is receiving steroid therapy for an immune related adverse event (irAE), the maximum dose delay could be 84 days to allow tapering of the steroid dose to ≤ 10 mg prednisone or equivalent.

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

7.7 Discontinuation of Treatment

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

7.8 Follow-Up Period

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

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

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version

5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Considerations

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

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

c. Once talazoparib dose is reduced, patients will continue at the new dose. No talazoparib 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, with the exception that if patient is receiving steroid therapy for an immune related adverse event (irAE), the maximum dose delay could be 84 days to allow tapering of the steroid dose to ≤ 10 mg prednisone or equivalent.

f. The assessment for discontinuation of talazoparib should be made separately from the assessment made for discontinuation of avelumab.

g. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for avelumab but not for talazoparib, treatment with talazoparib may continue if avelumab is discontinued, at the discretion of the treating physician. In the event that criteria are met subsequently for resumption of avelumab while treatment with talazoparib is ongoing, avelumab should be re-introduced on the first day of the next scheduled cycle of therapy. The above criteria would also apply if discontinuation criteria are met for talazoparib but not for avelumab.

If a patient receiving combination therapy meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the patient should discontinue both drugs.

See Section 7.4 for patient instructions.

8.3 Dose Interruptions – Avelumab

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

a. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the patient. Patients must be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.
- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment. - If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

b. Management of Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis	**Initial Management**	**Follow-up Management**
Grade 1	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1 to 2 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper < 10 mg per day over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). ** If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis. Permanently discontinue avelumab for Grade 4 diarrhea or colitis or recurrent Grade 3 diarrhea or colitis

Dermatological irAEs		
Grade of Rash	**Initial Management**	**Follow-up Management**
Grade 1 to 2	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids < 10 mg per day over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. ** If worsens: Treat as Grade 3 to 4.
Grade 3 to 4	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids < 10 mg per day over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). **
Pulmonary irAEs		
Grade of Pneumonitis	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Clinically re-assess at least every 2 weeks and resume at the discretion of the treating investigator If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids < 10 mg per day over at least 1 month, and then resume avelumab therapy following steroids taper ** If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.

Grade 3 to 4	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids < 10 mg per day over at least 1 month ** If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation	**Initial Management**	**Follow-up Management**
Grade 1	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2	Withhold avelumab therapy Increase frequency of monitoring to every 3 days. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater hepatitis.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy after corticosteroid taper. ** If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids < 10 mg per day over at least 1 month ** If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased	**Initial Management**	**Follow-up Management**
Grade 1	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.

Grade 2 to 3	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1 to 2 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids < 10 mg per day over at least 1 month, and resume avelumab therapy following steroids taper. ** If worsens: Treat as Grade 4.
Grade 4	Permanently discontinue avelumab therapy Monitor creatinine daily 1 to 2 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids < 10 mg per day over at least 1 month. **

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1 to 2 mg/kg/day prednisone or equivalent	Once improving, taper steroids < 10 mg per day over at least 1 month. ** If no improvement or worsening, consider additional

	Add prophylactic antibiotics for opportunistic infections.	immunosuppressants (e.g. azathioprine, cyclosporine A).

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH):	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.

	• Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. ****** • Add prophylactic antibiotics for opportunistic infections.	Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs	**Initial Management**	**Follow-up Management**
Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis, and encephalitis)		Permanently discontinue avelumab.
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1 to 2 mg/kg/day prednisone or equivalent	If improves to Grade ≤ 1:

	Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	Taper steroids < 10 mg per day over at least 1 month and resume avelumab therapy following steroids taper. **
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1 to 2 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids < 10 mg per day over at least 1 month. **
Grade 4	Permanently discontinue avelumab therapy 1 to 2 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids < 10 mg per day over at least 1 month **
**** Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency** **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

8.4 Dose Modifications – Talazoparib

Dose modifications should be made based on the observed toxicity, as summarized in the tables below. For any grade 4 toxicity, please contact Dr. Ferdinandos Skoulidis and Dr. Jennifer Marie Suga at S1900CMedicalQuery@swog.org.

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

Table 1: Renal Impairment Dose Modifications

Toxicity	Dose Modification
Grade ≥ 3	Hold protocol treatment until resolution to ≤ Grade 2, treatment may then resume at the next lower dose

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

Toxicity	Dose Modification
Hemoglobin Grade ≥ 3	Hold protocol treatment until resolution to ≤ Grade 2, treatment may then resume at the next lower dose.
Platelet count Grade ≥ 3	Hold protocol treatment until resolution to ≤ Grade 2, treatment may then resume at the next lower dose.
Neutrophil count Grade ≥ 3	Hold protocol treatment until resolution to ≤ Grade 2, treatment may then resume at the next lower dose.

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, talazoparib 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	

Talazoparib 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 talazoparib 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 talazoparib 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

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.

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Ferdinandos Skoulidis and Dr. Jennifer Marie Suga at S1900CMedicalQuery@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.

8.6 Adverse Event Reporting Requirements

TheRave® Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rule's evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

If you have questions about this process, please contact the SAE Program Manager 210-614-8808 or email adr@swog.org.

The CTEP-AERS electronic reporting system “Help” feature has detailed instructions in the section "Submitting Reports for RAVE Users".

8.7 Serious Adverse Event Reporting Requirements

a. **Definition and Purpose**

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (FDA, 21 CFR 312.32). See Table 8.6 for definition of a Serious Adverse Event (SAE) and reporting requirements.

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

b. **Reporting Method**

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

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

c. **When to report an event in an expedited manner**

Some adverse events require 24-hour notification (refer to Table 8.6) via CTEP-AERS.

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

When the adverse event requires expedited reporting, submit the report via CTEP-ARS within the number of calendar days of learning of the event specified in Table 8.6

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 participant has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 8.6. The investigational agent(s) used in this study are avelumab and talazoparib. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.6 (Section 8.6f.2).

Table 8.6:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention Talazoparib + Avelumab[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="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 8.6f.

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 documentation supporting the CTEP-AERS report to the SWOG Operations Office by fax 210-614-0006. Specific instructions will be sent by email to the reporting site by the SAE Program Manager.

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

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

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

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

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

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

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

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

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

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

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

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

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

9.0 STUDY CALENDAR

9.1 Talazoparib and Avelumab

NOTE: The study calendar is a good tool for a general snapshot of study requirements but does not replace details provided in the relevant sections of the protocol. Use the study calendar in conjunction with the detailed procedures and information in the protocol but not as the sole or primary source for managing this trial.

	Pre-Reg (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days)				At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [2]
REQUIRED STUDIES		Cycle 1	Cycle 2	Cycle 3	Subsequent Cycles [1]			
PHYSICAL								
History & Physical Exam	X	X	X	X	X	X	X [3]	
Weight & Performance Status	X	X	X	X	X	X	X [3]	
Patient Diary [5]		X	X	X	X	X		
Toxicity Notation		X	X	X	X	X	X [6]	X [6]
Smoking Status Assessment	X					X		
LABORATORY								
	If labs obtained w/in 14 days prior to tx, tests need not be repeated on C1D1.	Results up to 48 hours prior to Day 1 tx						
CBC/Diff/Platelets/ Hgb	X	X	X	X	X	X	X [6]	X [6]
Chemistry Panel [7]	X	X	X	X	X	X	X [6]	X [6]
TSH w/ Reflex to Free T4	X [13]		X [13]		X [13] (every other cycle)		X [6]	X [6]
Hepatitis B/ C viral load test	X [14]							

REQUIRED STUDIES	Pre-Reg (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days) Cycle 1	Cycle 2	Cycle 3	Subsequent Cycles [1]	At Off Tx	Off Tx FU Prior to Prog	Off Tx FU After Prog [2]
HIV viral load test	X [14]							
X-RAYS & SCANS								
CT or MRI for Disease Assessment [4]	X [4]		X [4] Week 6	X [4] Week 12	X [4]		X [4]	
Brain CT/MRI	X [8]			X [8] Week 12	X [8]		X [8]	
SPECIMEN SUBMISSION								
ctDNA Whole Blood		X [10] (pre-tx)		X [10]		X [10] (first progression & off protocol treatment)		
Buffy Coat /Plasma for Banking [11]	X		X [11]	X [11]	X [11] (cycle 4 only)	X [11] (first progression)		
TREATMENT (28-day cycle)								
Talazoparib [12]		X Days 1-28	X Days 1-28	X Days 1-28	X Days 1-28			
Avelumab [12]		X Days 1, 15	X Days 1, 15	X Days 1, 15	X Days 1, 15			

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

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines on the allowed protocol visits/treatment window as outlined in https://www.swog.org/clinical-trials/protocol-workbench. SWOG Best Practices allows for a +/- 3 day window for 28-day cycles.

Footnotes for Calendar 9.1 (Talazoparib and Avelumab):

[1] During continued treatment, items marked under physical and laboratory should be performed prior to every subsequent cycle, unless otherwise noted. Disease assessments and image submission are to take place on weeks 6 and 12 (± 7 days), and then every 8 weeks (± 7 days) thereafter, regardless of treatment delay. Treatment and evaluation will continue until any one of the criteria in Section 7.6 is met. If the patient remains on protocol treatment after progression due to clinical benefit in the opinion of the treating investigator (per Section 7.6), treatment schedule must continue per protocol.

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

[3] After off protocol treatment prior to progression, patients should be followed by repeating indicated studies every 8 weeks or more often as clinically indicated until progression. Disease assessment should continue per Section 7.3.

[4] CT or MRI (the same method used at pre-study to meet the eligibility criteria in Section 5.3) must take place on weeks 6 and 12 (± 7 days), and then every 8 weeks (± 7 days) thereafter, regardless of treatment delay, while on treatment. After off protocol treatment prior to progression, scans must take place every 12 weeks (± 7 days) until disease progression. The 6 weeks should start from sub-study registration. See Sections 5.3 and 7.3 for additional details.

[5] The CRA will review the Patient Diary at the end of each cycle (see Appendix 18.4).

[6] Assessments should continue if clinically indicated and until resolution of all acute adverse events.

[7] Chemistry panel (non-fasting) must include creatinine, LFTs (ALT, AST), and bilirubin.

[8] Brain CT/MRI is required per Sections 5.3 and 7.3. If patient has brain metastases at baseline, scans must use the same modality as baseline and be performed at week 12 (+/- 7 days) and every 8 weeks thereafter while on treatment. After off treatment prior to progression, patients should be followed by repeating brain CT or MRI every 12 weeks as clinically indicated until progression.

[10] See Section 15.3. Note: Kits must be ordered and will take up to 3 days to arrive.

[11] With patient's consent additional research blood draws will be collected per Section 15.4.

[12] See Section 7.0 for treatment details.

[13] TSH and if abnormal, reflex to Free T4 and other work up per investigator, should be performed as clinically indicated at pre-study. While on treatment, monitor thyroid function every other cycle. See Section 8.4 for avelumab dose modifications.

[14] See Section 5.1 for details.

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 (or millimeters).

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

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

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

c. **Notes on measurability**

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

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

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

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

5. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

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

10.2 Objective Status at Each Disease Evaluation

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

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

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

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

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

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

Notes on progression and new lesions:

1. For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled

assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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

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

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

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

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

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

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

Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not

progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.
8. Lymph nodes are considered one organ. Only two lymph nodes should be selected as target lesions. Other involved lymph nodes should be assessed and followed as non-target lesions.
9. "Paired" organs, i.e. lungs, kidneys and ovaries, are considered one organ.
10. Pleural-based lung lesions are considered part of the lung in determining target lesions (a maximum of two lung lesions should be selected), whereas pleural effusions/thickening can be reported as a separate site.

10.3 Best Response

This is calculated from the sequence of objective statuses.

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

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

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

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

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

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

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

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

10.4 Performance Status

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

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

10.5 Time to Death

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

10.6 Investigator-Assessed Progression-Free Survival

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

10.7 Progression-Free Survival by Central Review

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

10.8 Duration of Response (DoR)

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

10.9 Disease Control Rate at 12 Weeks (DCR12)

Disease control at 12 weeks is defined as a best response of CR, PR, UPR, or UCR by/at the second disease assessment at 12 weeks after registration (+/- 2 weeks), or stable disease at 12 weeks after registration (+/- 2 weeks). Patients with missing or delayed disease assessment at 12 weeks (+/- 2 weeks), at or before the disease assessment at 20 weeks (+/- 2 weeks) with documented lack of progression (CR, PR, UPR, UCR, or stable) are coded as having disease control at 12 weeks. Patients not known to have disease control at 12 weeks who have at least 12 weeks of follow-up will be coded as not having disease control at 12 weeks.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size with Power Justification

The co-primary objectives of the study are to evaluate the best objective response (CR, UCR, PR, UPR per 10.3) rate (ORR) and the disease control (CR, UCR, PR, UPR, or SD per 10.3) rate at 12 weeks after registration (DCR12) in patients treated with avelumab and talazoparib.

Eligibility is based on detection of pathogenic *STK11* genomic alterations (non-synonymous somatic mutations in *STK11* or bi-allelic loss on tumor genomic profiling using the FoundationOne assay – see Section 5.1).

The total accrual goal to the study is 40 eligible and evaluable patients. An interim analysis will take place on the first 20 eligible patients enrolled are evaluable for response (see details in section 11.2). Assuming that 10% of patients who are enrolled will be not eligible, the total accrual goal is 44 patients.

The sample size is based on a design with 90% power and 1-sided 0.05 level type I error to rule out an objective response rate (ORR) of 10% or less if the true ORR is 28% or greater and 90% power to rule out a DCR12 of 30% at the 5% level, if the true rate is 54%. However, the rules for concluding activity are based on a combination of these thresholds (see Table 2 for details).

The following table (Table 1) describes the power to conclude there is activity based on the underlying true response and stable disease rates by 12 weeks after registration (recalling that disease control is the combined response and stable disease rates). The properties of this design are summarized in Table 2.

Table 1: Probability of concluding activity of talazoparib and avelumab

True Response Rate	Power for RR alone*	True Disease Control Rate			
		30%	35%	45%	55%
10%	4	6	11	31	47
15%	23	25	29	51	73
20%	56	56	56	68	87
25%	81	81	81	84	94
30%	94	94	94	94	98

***** Provided for comparison if the study success rules did not include DCR and were based on RR alone

The expected prevalence of the *STK11* biomarker is 17%. Sites are notified of a patient's sub-study assignment by the SWOG Statistical and Data Management Center (SDMC) after the results of the biomarker testing have been reported to the SDMC. As described in

LUNGMAP Section 11.0 (the Lung-MAP screening protocol), patients with biomarkers matching only this study will be assigned to this study and sub-study assignment will be based on randomization for patients eligible for multiple biomarker-driven sub-studies. The frequency of patients assigned to this sub-study will depend on the other biomarker-driven sub-studies actively accruing while this study is accruing and could be less than the percentages eligible for the sub-studies.

The expected average monthly accrual rate is 3 patients per month. The anticipated duration of accrual is 15-19 months, depending on the need for a temporary closure. The anticipated duration of follow-up to the final analysis is 6 months after the study is closed to accrual.

11.2 Analysis Plan

The interim analysis will take place when the first 20 enrolled eligible patients are evaluable for response. Patients will be considered evaluable if they receive at least one dose each of talazoparib and avelumab and satisfy one of the following: 1) had a response reported, 2) have gone off protocol treatment in the absence of response, or 3) have submitted at minimum the first 4 disease assessments indicating lack of response. Patients not known to have a response will be coded as non-responders. Accrual will be placed on a temporary hold if all patients in the interim analysis set have submitted data for second scheduled disease assessment and the rule to continue accrual has not be met.

The rule for continuing past the 1st stage is based on an assessment of objective response alone. The observation of 2 or more objective responses (CR or PR, confirmed or unconfirmed) in the would be considered sufficient evidence to continue accrual up to a total of 40 eligible patients who received at least one dose of talazoparib and avelumab.

Table 2. Likelihood of continuing to 2nd stage

True Probability of response	Probability of continuing
5%	25%
10%	61%
15%	82%
20%	93%
25%	98%
30%	99%

If the study meets the criteria to continue to full accrual:

- the observation of at least 8 patients with a response (20% response rate) would be considered evidence to rule out a response rate of 10%.
- the observation of at least 18 patients with disease control at 12 weeks (45% or greater) would be considered evidence to rule out a DCR12 of 30%.

The thresholds for interpretation of activity is based on these thresholds but allows for interpretation of activity based on a minimal level of responses and the disease control rate threshold. The study would be considered to have provided sufficient evidence to study talazoparib and avelumab further if the criteria in the following table are met:

Table 3: Criteria for interpretation of study data at final analysis

Response Evaluation # responses	Disease Control at 12 weeks evaluation # w/ disease control **< 18 w/ DCR12**	 **≥18 w/ DCR12**
< 4	No evidence of activity	No evidence of activity
4-7	No evidence of activity	**Evidence of activity**
≥ 8	**Evidence of activity**	**Evidence of activity**

Secondary objectives will include an assessment of the frequency and severity of toxicities, estimation of the distribution of progression-free survival (PFS), overall survival (OS), and duration of response among responders.

Binary proportions and associated confidence intervals will be calculated. The method of Kaplan-Meier will be used to estimate survival distributions and the Brookmeyer-Crowley method will be used to estimate confidence intervals around medians.

With 40 eligible patients, binary proportions (response rates, DCR12, PFS and OS at landmark times) can be estimated to be within 16% with 95% confidence.

12.0 DISCIPLINE REVIEW

12.1 Radiology Review

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

a. To ensure the highest standards and consistency between different centers, all scans for disease assessment (baseline, interim and end of treatment scans) must be submitted to the National Cancer Institute's National Clinical Trials Network (NCTN) Imaging and RT Quality Assurance Service Core (IROC) in Ohio for centralized review (Section 15.5).

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

c. Details of submission of scans to IROC for centralized review and on the central review process are listed in Section 15.5 and **LUNGMAP** Appendix 18.2f.

13.0 REGISTRATION GUIDELINES

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

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

13.1 Registration Timing

Initiation of treatment must be planned to start no more than 10 calendar days after sub-study registration.

13.2 Investigator/Site Registration

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

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

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

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

14.2 Master Forms

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

14.3 Data Submission Procedures

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

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

Rave role requirements:
- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and

- Rave Read Only role must have at a minimum an Associates (A) registration type.

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

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

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

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

a. 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.

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

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

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

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.
To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

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

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS OF **S1900C** REGISTRATION, SUBMIT:

Vital Status Form

S1900C Eligibility Criteria Form

S1900C Onstudy Form

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

Smoking Status Assessment Form

Baseline Tumor Assessment Form (RECIST 1.1)

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

If needed, RT summary and/or planning document*

If needed, radiology report from brain CT/MRI*

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

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

b. IF PATIENT CONSENTS, SUBMIT SPECIMENS:

Specimens as specified in Section 15.0

c. WITHIN 15 DAYS AFTER EACH CYCLE (CYCLE = 28 DAYS) OF TREATMENT, SUBMIT:

Vital Status Form

S1900C Treatment Form

S1900C Adverse Event Form*

If needed, Immune-Related Adverse Event Form

S1900C Laboratory Values Form

For Cycle 1 only: Submit the **S1900C** Pre-Treatment Laboratory Values Form.

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

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

Vital Status Form

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 Section 15.5.

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

Vital Status Form

Off Protocol Treatment Notice documenting reasons for off protocol treatment

Smoking Status Assessment Form

Forms specified in Section 14.4c.

f. WITHIN 30 DAYS, ONCE OFF PROTOCOL TREATMENT EVERY 6 MONTHS FOR THE FIRST 2 YEARS FROM **S1900C** REGISTRATION, THEN AT THE END OF YEAR 3 FROM SUB-STUDY REGISTRATION SUBMIT:

Vital Status Form

Advanced NSCLC Follow-Up Form

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

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

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

Vital Status Form

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 Section 15.5.

h. WITHIN 30 DAYS OF KNOWLEDGE OF DEATH:

Vital Status Form

Submit the Notice of Death documenting death information and **S1900C** End of Study form. In addition, if the patient was still on protocol treatment, submit materials specified in Section 14.4e or if patient was no longer on treatment, submit a final Advanced NSCLC Follow-Up Form.

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

WITHIN 15 DAYS OF PROGRESSION/RELAPSE:

Submit the Request for New Sub-Study Assignment Form under the patient's screening protocol (**LUNGMAP**) in Rave®. Continue follow-up on **S1900C** per Section 9.0. See Section 14.0 of the screening protocol for additional data submission requirements following request for new sub-study assignment.

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

Vital Status Form

S1900C End of Study Form

15.0 SPECIAL INSTRUCTIONS

15.1 Specimen Flow Diagram

Please refer to Section 15 of **LUNGMAP** for the specimen flow diagram for the screening protocol.

15.2 SWOG Specimen Tracking System (STS)

See **LUNGMAP** Section 15.1 for SWOG Specimen Tracking System (STS) instructions.

15.3 LUNGMAP ctDNA Assay – Peripheral Whole Blood (***REQUIRED FOR PATIENTS***)

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

a. Kit Ordering

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

- Call FMI Client Services at 1-888/988-3639 or email request to lung.MAP@FoundationMedicine.com
- Site must identify itself as a participant in the SWOG Lung-MAP **S1900C** sub-study and request the "Lung-MAP ctDNA Clinical Trial Kit"
- Reference the FMI Study ID: FoundationOneLiquidDx-AMC-PRO-20-1496
- Provide the following information:
  - Treating physician's name
  - Treating physician's email address
  - Contact name
  - Contact email address
  - Contact phone
  - Address to which kits should be sent
  - Number of kits needed (one per patient per timepoint)

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

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

b. Timepoints

Collect blood at:

- After sub-study registration and prior to treatment initiation
  - Recommended to collect on Cycle 1 Day 1 (prior to treatment) during other labs to lessen patient visits.

    Note: This is a separate requirement for a ctDNA whole blood specimen for all patients registered to **S1900C**, regardless of whether or not there was a ctDNA blood collection for **LUNGMAP**.

- Cycle 3 Day 1 (prior to treatment)
- First progression after study treatment
  - Collection must be within 14 days after site learns of progression and prior to starting non-protocol treatment.
- Off protocol treatment

Note: If the first progression after study treatment and the off protocol treatment timepoints occur at the same time, only a single specimen is to be collected.

c. Specimen Collection and Shipment Instructions

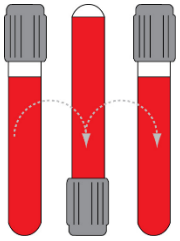
Specimen must be logged via the SWOG Specimen Tracking System.

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

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

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

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



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

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

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

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

d. Specimen Usage

Cell-free, circulating DNA will be isolated from the plasma component of the whole blood. Using a hybrid-capture, next-generation sequencing technology (developed by Foundation Medicine), alterations in clinically significant cancer genes (oncogenes and tumor suppressor genes) will be identified and quantitated relative to wild-type sequences. Tumor-specific alterations will include point mutations, small insertions and deletions, chromosomal rearrangements and copy number/amplification events in (**LUNGMAP** ctDNA Assay) including an assessment of tumor mutation burden (TMB) will be conducted using ctDNA. A full proposal will be developed, reviewed, and approved by SWOG and CTEP once funding has been obtained.

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

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

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

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

1. Buffy Coat and Plasma:

Specimens must be collected at the following times.

- Pre-study (after consenting and prior to treatment initiation on sub-study)
  Note: If a patient provided buffy coat and plasma for **LUNGMAP** and the blood collection was within 42 days prior to the sub-study registration, then no additional pre-study blood specimen is required.
- Cycles 2, 3, 4 (at the same time as lab collection, prior to the start of cycle treatment) - Patients that go off protocol treatment are not required to continue to submit specimens.
- First progression after study treatment.

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

Spin the plasma in the 15-mL centrifuge tube at 800 x g for an additional 10 minutes. Avoiding any pelleted material, pipette the plasma into 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 must be shipped to the SWOG Biospecimen Bank on dry ice. Frozen specimens may be shipped in batches – refer to Section 15.4b.

b. Specimen Collection, Submission, and Labeling Instructions

Samples for multiple patients may be shipped in batches to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201, at least every 3 months (if not more frequently), with a maximum of 5 patients' samples included per batch.

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

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

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

15.5 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 central review.

a. CT, PET/CT, and/or MRI images must be submitted to IROC Ohio for central review. See Section 7.3 and 9.0 for timepoints and details.

The same imaging modality used for the pre-treatment exam must be used for the post-treatment exams (see **LUNGMAP** Section 10.1). Each exam should be performed per Appendix 18.2f of **LUNGMAP**. IROC will perform a QC of the imaging exams.

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

Clinical management and treatment decisions will be made by the treating physician based on local site assessments and other clinically 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 review, including image acquisition parameters and image submission instructions, can be found in Appendix 18.2f of **LUNGMAP**.

b. TRIAD Digital Image Submission

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

TRIAD 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.

1. TRIAD Access Requirements:

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

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

2. TRIAD Installation:

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

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

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

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

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

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

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

Publication and Industry Contact

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

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

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

    1. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

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

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

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

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

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

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

E-mail: ncicteppubs@mail.nih.gov

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

Monitoring

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

Trial Master File

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

Confidentiality

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

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18.0 APPENDIX

18.1 New York Association Classification

18.2 Monitoring Plan

18.3 Instructions for the SWOG Biospecimen Bank

18.4 Patient Diary – Talazoparib

18.5 Patient Drug Information Handout and Wallet Card

18.6 Site Temperature Excursion Report Form

18.1 New York Heart Association Classification

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

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

18.2 Monitoring Plan

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

18.3 Instructions for the SWOG Biospecimen Bank

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

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

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

18.4 Patient Diary – Talazoparib **SWOG Study: S1900C**

Site Personnel Instructions

- Patient numbers should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient.
- Ensure that patient clearly understands the guidelines for self-medication.
- Patient should be given enough supply to last until their next study visit.
- Unused drug and/or empty bottles should be returned to the site at the next study visit.

Please review the following with the patient:

- Cycle, Start Date and Start Time information with the patient. If possible, have the patient document their first dose in the appropriate calendar box.
- Patients and their caregivers should be advised that talazoparib is a toxic substance and that gloves should always be used when handling the talazoparib capsules.
- Patient's dose schedule: Talazoparib should be taken once a day, as close to the same time each day as possible (preferably in the morning). Provide patient with the instructions on how to document this schedule appropriately.
- Talazoparib can be taken with or without food.
- How to document vomited, missed, or skipped doses in the specific areas provided.

SWOG Patient ID _____ Patient Initials (L, F, M) _____ **SWOG Study #** _____
Cycle: _____ Start Date: _____ Start Day (circle one): Sun M Tu W Th F Sat

Instructions for the patient:
Record the date and time of the talazoparib capsules you take each day on this calendar. You should:

- Always use gloves when handling the talazoparib capsules.
- Take your medication once a day, at the same time each day (preferably in the morning).
- Put the date in the box on the calendar and note the time of the dose each day.
- Check off if the dose was taken or not.
- Talazoparib can be taken with or without food.
- Swallow the capsules whole. Do not chew. Do not take any capsules that are broken or cracked.
- Document any changes to taking the doses in the comments section provided below.
  - If you forget to take the dose at your usual time, dose can be taken as long as there is 12 hours before your dose the next day.
  - If you miss a day's dose, do not "make it up." Mark it as a "missed" dose with the date and time. Take the normal dose the next day.
  - If you vomit a dose, the dose should not be re-taken. Record this as a "vomited" dose with the date and time.
  - If you accidentally take an extra dose during a day, skip the next day's dose. Record this as an "extra dose."
- If you develop any side effects from the capsule, mark the side effect on the comments section provided with the date and time you developed the side effect.

Storage:
Talazoparib capsules are to be stored at controlled room temperature, 59-86°F.

Date	Was dose taken?	What time?	Comments
Day 1 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 2 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 3 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 4 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 5 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 6 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 7 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 8 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 9 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 10 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 11 ____/____/____	□ Yes □ No	____:____ am/pm	

Day 12 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 13 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 14 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 15 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 16 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 17 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 18 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 19 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 20 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 21 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 22 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 23 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 24 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 25 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 26 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 27 ____/____/____	□ Yes □ No	____:____ am/pm	
Day 28 ____/____/____	□ Yes □ No	____:____ am/pm	

18.5 PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #:**	
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	**Talazoparib + Avelumab**

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by National Cancer Institute.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet. **These are the things that you need to know:**

Talazoparib and avelumab may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including:

- medicines you are taking before this clinical trial,
- medicines you start or stop taking during this clinical trial,
- medicines you buy without a prescription (over-the-counter remedy),
- herbal supplements such as St. John's Wort.

Please bring your medication bottles or an updated medication list with you.

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

These are the things that your healthcare providers need to know:

- The proteins in question are P-gp inhibitors and BCRP. Talazoparib is moved in and out of cells/organs by these transport proteins and may be affected by other drugs that strongly inhibit these transport proteins. Use of strong P-gp and BCRP inhibitors 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).
- Patients must not receive any live attenuated vaccinations while on study treatment.

These are the things that you and your healthcare providers need to know:

Talazoparib must be used very carefully with other medicines that use certain transport proteins to be effective. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors of the transport proteins P-gp and BCRP.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Make sure your doctor knows to avoid certain prescription medications.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

Patient Drug Interaction Wallet Card

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EMERGENCY INFORMATION

Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

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Tell your doctors **before** you **start** or **stop** any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following drugs if possible:

Talazoparib may interact with drugs that use certain transport proteins in your body.

Avoid any medicines that are considered strong inhibitors of P-gp and BCRP while taking talazoparib.

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

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DRUG INTERACTIONS

Carry this card with you at all times

Talazoparib interacts with transport proteins P-gp and BCRP and must be used very carefully with other medicines that interact with this transporter.

Your healthcare providers should be aware of any medicines that are considered strong inhibitors of P-gp and BCRP.

Before prescribing new medicines, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.

Version SEP 2019

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

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For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

18.6 Site Temperature Excursion Report Form

For information on talazoparib and avelumab storage temperature excursion, please refer to Section 3.0 and submit this form to Pfizer.

Form Version: 23Dec2016

Submit completed form to: GCSTempExcursionSupport@pfizer.com

SECTION 1. Study Information		
Protocol Number		
Site Number		
Country		
Investigational Product Name or Number[1]		
Principal Investigator First and Last Name / Title		
Form Completed by <First and Last Name / Title (Printed)>		**Date: <***dd-Mmm-yyyy***>**

SECTION 2. Investigational Product and Dispensing Information		
Date of Temperature Excursion[2]	*<dd-Mmm-yyyy>*	
Temperature Log that Shows the Date and Duration of this Excursion Only[3]	***Provide relevant document(s) as a separate attachment when submitting this form.***	
Lot (PReq) Number of Impacted IP[4]	*<format XX-YYYYYY>*	
Kit Number(s) and/or Container Number(s) of Impacted Investigational Product (if applicable)[5]		
Were any Affected Kit(s) and/or Container(s) Dispensed to Subjects[6]	☐ **No** ☐ **Yes** **If yes – List the affected Kit Numbers and/or Container Numbers and dates they were dispensed.**	
	Kit and/or Container Number	*Date Dispensed (dd-Mmm-yyyy)*
	N/A	*N/A*
	N/A	*N/A*
Date of Next Subject Visit[7] if applicable	*<dd-Mmm-yyyy>*	
Distribution and/or IRT System Used to Distribute and/or Dispense investigational product (N/A for PCH)		
Storage Condition on Label		

Lot(s)/Kit(s) that had Excursion are Now Returned/Maintained in Acceptable Storage Condition	☐ **No** ☐ **Yes**

SECTION 3. Temperature Excursion Decision (To be completed by Pharmaceutical Sciences (PharmSci)/ PCH supply chain only)		
Kit Number(s) and/or Container Number(s) of Impacted Investigational Product (if applicable)	**Summary of Excursion**	**Investigational Product Acceptable for Use**
		☐ **Acceptable** ☐ **Not Acceptable**
		☐ **Acceptable** ☐ **Not Acceptable**
		☐ **Acceptable** ☐ **Not Acceptable**
Form Completed by < PharmSci/PCH Representative First and Last Name/Title (Printed)>		
Date	*(dd-Mmm-yyyy)*	