ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A092104

A RANDOMIZED PHASE 2/3 STUDY OF OLAPARIB PLUS TEMOZOLOMIDE VERSUS INVESTIGATOR'S CHOICE FOR THE TREATMENT OF PATIENTS WITH ADVANCED UTERINE LEIOMYOSARCOMA AFTER PROGRESSION ON PRIOR CHEMOTHERAPY

[X]	**Update:**	[ ]	**Status Change:**
[X]	Editorial/Administrative changes	[ ]	Activation
[ ]	Eligibility changes	[ ]	Closure
[ ]	Therapy/Dose Modifications/Study Calendar changes	[ ]	Suspension
[ ]	Scientific/Statistical Considerations changes	[ ]	Reactivation
[ ]	Correlative Science/BioMS changes		
[X]	Informed Consent changes		
[X]	Other: Updated CAEPR for Olaparib		

The changes included in this update to A092104 have been made in response to the NCI Action Letter from Dr. Steve Gore (steve.gore@nih.gov) for Olaparib. This Action Letter is posted on the A092104 study page on the CTSU website. A revised CAEPR for Olaparib with new risks has been added to the protocol. Additionally, Pazopanib risks have been replaced with standard of care risks in the protocol. Therefore, the model consent form has been revised to incorporate the new risks, consistent with the NCI Model Consent Template instructions.

No recommended level of IRB review is provided by the Alliance as the CIRB is the IRB of record for this trial. This amendment must be implemented within 30 days after posting.

A consent form addendum will need to be signed by all patients currently receiving treatment or having treatment held with Olaparib or Pazopanib. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL

Cover Page

- Dr. Matthew Ingham has replaced Dr. Brian Van Tine as Study Chair. All contact information has been updated accordingly.
- The NRG Oncology Study Chair email contact information has been updated.

- Kayla Kroll has replaced Brandon Bright as the Data Manager and the contact information has been updated accordingly.
- The Protocol Coordinator's contact information has been updated per Alliance protocol template.

Study Resources
David Chan has replaced Barb Todaro as the Pharmacy Contact. All contact information has been updated accordingly.

Section 9.3.1 (Late Phase 2 and Phase 3 Studies)
The SAE Reporting Table has been updated to the most current CTEP version dated August 30, 2024.

Section 9.3.2 (Expedited AE reporting timelines defined)
- This sub-section has been completely removed as the information no longer pertains to the updated SAE Reporting Table in Section 9.3.1.
- The remaining sub-section has been renumbered.

Section 9.4.1 (Comprehensive Adverse Events and Potential Risks list (CAEPR) for Olaparib (AZD2281, NSC 747856))
This section has been revised to include the updated olaparib CAEPR (Version 2.7 ~~6~~, ~~June 5, 2023~~ July 9, 2025) provided by NCI CTEP. Changes from Version 2.6 to Version 2.7 include the following:
- Added New Risk:
  - Rare but Serious: Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia (AIHA)); Blood and lymphatic system disorders - Other (pure red cell aplasia (PRCA)); Hepatobiliary disorders - Other (drug-induced liver injury (DILI))
- Increase in Risk Attribution:
  - Changed to Less Likely from Rare but Serious: Vascular disorders - Other (venous thromboembolism)
  - Changed to Rare but Serious from Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Lymphocyte count decreased
- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Abdominal pain; Anorexia; Diarrhea
  - Changed to Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution from Less Likely: Abdominal distension; Edema Limbs; Mucositis oral; Muscle cramp; Rash maculo-papular; Urinary tract infection
- Deleted Risk:
  - Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Bone pain; Flushing; Hypermagnesemia; Hypothyroidism; Renal and urinary disorders - Other (decreased glomerular filtration rate)
- Provided Further Clarification:
  - Footnote #2 is now added as "Autoimmune hemolytic anemia (AIHA) and Pure red cell aplasia (PRCA) have been reported in clinical trials as potential and identified risks when Olaparib is used in combination with durvalumab."
  - Footnote #3 is now added as "Venous thromboembolism includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis."
  - Footnote #4 is now added as "Rash includes exfoliative rash, generalized erythema, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic."

Section 9.4.2 (~~Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pazopanib (GW786034, NSC 737754))~~ Adverse Event List for Pazopanib

- The title of the section has been updated in accordance with the removal of the Pazopanib CAEPR.
- The Pazopanib CAEPR has been completely removed and replaced with Pazopanib AE risk tables as per a recent change in CTEP policy, protocols should no longer include the CAEPR for Standard of Care agents or regimens being used per FDA label.

10.4 (Pazopanib (GW786034, Votrient, NSC#737754))

Subsection 'Adverse Events' has been updated to support the removal of the CAEPR in Section 9.4.2 and now states, "See ~~CAEPR in~~ Section 9.4.2."

Section 13.9 (Inclusion of Women and Minorities)

In both paragraphs, "gender" has been replaced with "sex" in accordance with the January 20, 2025, Executive Order 14168, "Defending Women from Gender Ideology Extremism and Restoring Biological Truth to the Federal Government."

UPDATES TO THE MODEL CONSENT FORM:

In Drug Risks, the table under the '**Possible Side Effects of Olaparib**,' has been updated and with the following risk list changes:

- The Table Version date has been updated from ~~June 5, 2023~~ to July 9, 2025
- Added New Risk:
  - Rare: Damage to the liver which may cause yellowing of the eyes and skin, swelling
- Increase in Risk Attribution
  - Changed to Occasional from Rare: Blood clot
- Decrease in Risk Attribution:
  - Changed to Occasional from Common: Pain; Diarrhea; Loss of appetite
  - Changed to Rare from Common: Rash
  - Changed to Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from the Risk Profile): Bloating; Sores in the mouth which may cause difficulty swallowing; Swelling of arms, legs; Infection which may cause painful and frequent urination

In Drug Risks, the risk tables under the '**Possible Side Effects of Pazopanib**,' have been completely removed and replaced with standard of care, 'Usual Treatment Risks' as per a recent change in CTEP policy. In the standard of care risks, there is an added new risk: Non-healing wound.

INFORMED CONSENT ADDENDUM:

A new informed consent addendum has been added to reflect the new or additional information for Olaparib with this update. This addendum is intended to be signed by all patients currently receiving treatment or having treatment held with Olaparib.

A new informed consent addendum has been added to reflect the new or additional information for Pazopanib with this update. This addendum is intended to be signed by all patients currently receiving treatment or having treatment held with Pazopanib.

A replacement protocol, model consent, and informed consent addendum have been issued.

This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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ALLIANCE A092104

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NCI-supplied agent: Olaparib (NSC# 747856, IND #[redacted] IND holder: DCTD, NCI; Commercial agents: Temozolomide (NSC# 362856), Trabectedin (NSC# 684766), Pazopanib (NSC# 737754)

ClinicalTrials.gov Identifier: NCT05432791

Study Chair
Matthew Ingham, MD
Perlmutter Cancer Center
NYU Langone Health
160 E 34th Street, 7th Floor
New York City, NY 10016
Tel: 202- 285-4944
matthew.ingham@nyulangone.org

NRG Oncology Study Chair
Martee Hensley, MD
Memorial Sloan-Kettering Cancer Center
300 E. 66th St, Office 1355
Tel: 646-888-4222 Fax: 646-888-4268
hensleym@MSKCC.ORG

Experimental Therapeutics Rare Tumors Committee Co-Chair
Pamela Munster, MD
Pmunster@medicine.ucsf.edu

Experimental Therapeutics Rare Tumors Committee Co-Chair and Community Oncology Co-Chair
Gary Schwartz, MD
gks37@case.edu

ECOG-ACRIN Study Champion
Kristen N. Ganjoo, MD
kganjoo@stanford.edu

Primary Statistician
Sumithra Mandrekar, PhD
Tel: 507-266-6724
mandrekar.sumithra@mayo.edu

Secondary Statistician
Jake Allred, MS
Tel: 507-266-2874
allred@mayo.edu

Protocol Coordinator
Beth Smith
etrtprotocols@alliancenctn.org

Data Manager
Kayla Kroll
Tel: 507-293-1767
kroll.kayla@mayo.edu

Participating Organizations

Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG

Study Resources:

Expedited Adverse Event Reporting https://ctepcore.nci.nih.gov/ctepaers	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

Protocol Contacts:

A092104 Nursing Contact
Lisa Kottschade, APRN, MSN, CNP
kottschade.lisa@mayo.edu

A092104 Pharmacy Contact
David Chan, PharmD, PhD
dchan@uic.edu

Alliance Biorepository at Washington University (WUSTL)
Washington University as St Louis
BJC Institute of Health 425 S. Euclid Ave,
Room 5120
St. Louis, MO 63110-1005
Tel: 314-747-4402
alliance@email.wustl.edu

Pharmaceutical Management Branch, CTEP/DCTD/NCI
(240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email
PMBAfterHours@mail.nih.gov

Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, and (where applicable) Data Manager, (cc Protocol Coordinator)
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@alliancenctn.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@alliancenctn.org
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Washington University (WUSTL)
Questions regarding drug supply	PMB
Questions regarding drug administration	Pharmacy Contact

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 Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://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 by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org 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_SYS TEM/ 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). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
Institutions will obtain the following supplies from the CTSU website: PRO CTCAE can be obtained by downloading the booklet from the protocol-specific page on the CTSU website.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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Eligibility Criteria (see Section 3.0)

Histologically confirmed leiomyosarcoma of uterine origin

Metastatic or locally advanced/unresectable disease

Measurable disease per RECIST v1.1 (See §11.0)

Not pregnant and not nursing (See §3.2.3)

Age ≥18

ECOG Performance Status ≤ 2

Prior Treatment:

- Prior progression on, or intolerance to, at least two prior lines of systemic therapy for advanced uLMS, one of which was an anthracycline (anthracycline monotherapy or combination). Adjuvant chemotherapy will qualify as a prior line of treatment. Endocrine treatment will not qualify as a prior line of treatment.
- No prior treatment with any PARP inhibitor, temozolomide or dacarbazine (IV analogue of temozolomide).
- No prior treatment with at least one of the agents included on the investigator's choice arm: trabectedin, pazopanib (or both).
- Patients must have recovered to baseline or ≤ grade 1 per CTCAE version 5.0 from toxicity related to any prior treatment, unless adverse events are clinically nonsignificant and/or stable on supportive therapy, with the exception of fatigue (which should be ≤ grade 2), alopecia and/or endocrinopathies related to prior immunotherapy which are controlled with hormone replacement.
- Patients must have completed all prior anti-cancer treatment ≥28 days from registration.

Prior Surgery:

- Patients may not have undergone major surgery (related or unrelated to their cancer diagnosis) ≥28 days of registration. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

No uncontrolled hypertension, ventricular arrhythmias or recent myocardial infarction (See §3.2.9)

Comorbid conditions (See §3.2.10)

Concomitant medications (See §3.2.11)

No use of concurrent strong CYP3A4 inducers/inhibitors

Must be able to speak and/or read English or Spanish to complete PRO-CTCAE surveys.

Deemed appropriate for treatment with either trabectedin or pazopanib per the treating investigator. For all patients, prior to randomization and as part of eligibility, the investigator must select the agent which the patient would receive if assigned to the investigator's choice arm.

Required Initial Laboratory Values	
ANC:	≥ 1500/mm^3
Platelet count:	≥ 100,000/mm^3
Creatinine[1]:	≤ 1.5 x ULN
Hemoglobin[2]:	≥ 9 g/dL
Total bilirubin[3]:	≤ 1.5 x ULN
AST/ALT:	≤ 3.0 x ULN

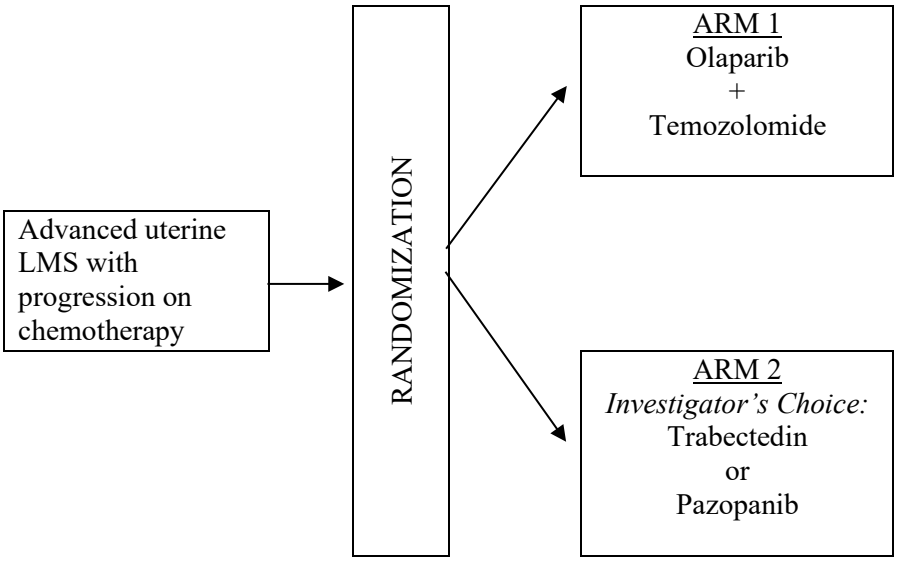
[1]If creatinine > 1.5* ULN, then CrCl must be > 50 mL/min, per Cockcroft-Gault method.

[2]No transfusions ≤ 14 days before C1D1.

[3]If documented Gilbert's: ≤ 2.0 x ULN.

Schema

1 Cycle = 21 Days



Stratification factors: ECOG PS (0-1 versus 2) and Prior Lines (2 versus 3 or more)

70 patients will be enrolled to the Phase II portion of the trial. Enrollment will be paused at that time for treatment evaluation (see Section 13.2.2)

Treatment is to continue until disease progression or unacceptable adverse event(s). Patients discontinuing their initial treatment for reasons other than progressive disease will continue following the Study Calendar for disease assessments until progressive disease is documented. Upon progression, patients will be followed for information on subsequent anti-cancer treatment and survival every 3 months for the first 2 years and every 6 months thereafter until 5 years post-randomization or death, whichever comes first. Information on the first subsequent anti-cancer treatment and survival status must be collected.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Table of Contents

1.0 BACKGROUND

uLMS Background: Uterine leiomyosarcoma (uLMS) is an aggressive subtype of soft tissue sarcoma with frequent metastatic relapse. Advanced uLMS is treated with chemotherapy. The most active regimens used in the first- and second line settings (doxorubicin or the combination of gemcitabine and docetaxel) provide objective response rates (ORR) of 15-35% and median PFS of 4-6 months [1,2]. The cytotoxic agent trabectedin and the angiogenic receptor tyrosine kinase inhibitor pazopanib are the remaining therapies approved for uLMS, are used after progression on the above chemotherapy regimens, and provide progression-free survival (PFS) of 3-4 months, ORR 11%, and no improvement in overall survival (OS). Dacarbazine and temozolomide are also used in later-line treatment of uLMS. Immunotherapy with checkpoint blockade has proven ineffective, and no targeted treatment approach has shown significant clinical activity to date. The current landscape of treatment options for uLMS is summarized in **Table 1**.

Agent	ORR (%)	Median PFS (mos)	Median OS (mos)
First-line:			
Gemcitabine+ Docetaxel[1]	27-36%	4.4-6.7	14.7-16.1
Doxorubicin[3]*	14-19%	4.6-5.4	12.8-17.6
Later-line:			
Trabectedin[4]	11%	4.0	13.4
Pazopanib[5]	11%	3.0	17.5
Dacarbazine[4]	9%	1.5	12.9
Table 1: Standard-of-care treatment for uLMS (* all sarcoma)			

uLMS Harbors HR-deficiency: Recent reports from several groups have established that LMS, and particularly uLMS, harbors characteristic defects in the homologous recombination (HR) DNA repair pathway – i.e. features of BRCAness, similar to ovarian, breast, prostate and pancreatic cancers. HR-deficient tumors may be sensitive to PARP inhibitor-based treatment strategies. Poly-ADP ribose polymerase (PARP) inhibitors trap PARP at sites of DNA damage resulting in double-stranded DNA breaks and stalled replication forks. These DNA lesions cannot be effectively repaired in HR-deficient cells, resulting in progressive genomic instability and cell death.

In a whole exome and transcriptomic sequencing study of 49 LMS patients, deleterious alterations in HR pathway genes were found in the majority of tumors [6]. Enrichment of Alexandrov-COSMIC mutational signature AC3, associated with defective HR repair, was found in 57% of cases. In clonogenic assays, LMS cell lines contained multiple alterations in HR genes and were responsive to olaparib in a dose-dependent fashion [6]. In a separate cohort of 170 LMS patients from The Ohio State University and TCGA, deleterious alterations in HR genes were found in 23% of patients with uLMS and 15% with non-uterine LMS, with BRCA2 loss occurring in 10% of uLMS cases [7]. These patients derived significant benefit from off-label olaparib [7]. In an analysis of 211 LMS cases from MSKCC, deleterious alterations in HR pathway genes were enriched in uLMS as compared non-uterine LMS [8]. Approximately 18% of uLMS patients harbored an HR pathway alteration, and the proportion of uLMS cases with an HR-deficient mutational signature was among the highest of all tumor types in the TCGA. uLMS was also found to harbor high homologous recombination deficiency (HRD) scores as compared other tumor types. Lastly, in a pan-cancer analysis of germline and somatic BRCA alterations and their relevance to initiation and progression of various cancers, uterine sarcoma harbored the highest rate of homozygous BRCA2 deletion and was hypothesized by the authors to represent a previously unrecognized HR-deficient cancer type [9].

Preclinical Data and Completed Phase II Study: We conducted preclinical investigations with PARPi and PARPi plus chemotherapy combinations in uLMS which revealed significant clinical

activity for the combination of low-dose temozolomide (T) and olaparib (O, a PARPi) in uLMS models [10]. The combination was markedly more active than either monotherapy. T, which induces single-stranded DNA breaks, may potentiate PARP trapping. The preclinical data has been published elsewhere [10].

We therefore conducted an open-label, single-arm, phase II study of T + O in previously treated uLMS (NCI Protocol 10250) which demonstrated an overall ORR of 27% and median PFS of 6.9 months [11]. These findings compare favorably with efficacy of the two FDA-approved agents for uLMS after progression on initial chemotherapy of doxorubicin and gemcitabine/docetaxel: trabectedin and pazopanib. Trabectedin is generally considered third-line standard of care (SOC) for uLMS. In a subset analysis of the pivotal, randomized, registration-directed phase III study, trabectedin provided an ORR of 11%, median PFS of 4.0 months and median OS of 13.4 months for uLMS. In a subset analysis of patients with uterine sarcoma receiving pazopanib in the randomized, registration-directed phase III study (86% of whom had uLMS), the response rate was 11%, median PFS was 3.0 months and median OS was 11.0 months [5]. As noted above, the preclinical data suggest that the olaparib and temozolomide combination is markedly more effective than either monotherapy. There is no single-agent clinical data available for olaparib in uLMS or sarcoma. Temozolomide is the oral analogue of dacarbazine, and these two agents share the same active metabolite. In randomized, controlled uLMS trials, dacarbazine is associated with an ORR of 9% and PFS of 1.5 months [5]. There is limited data available on temozolomide monotherapy in uLMS, and the data that exists is limited to small historical studies.

	n (%)
Female	22 (100%)
Median age	55
Range	39-71
ECOG PS	
0	7 (32%)
1	15 (68%)
Race	
White	17 (77%)
Black/African American	3 (14%)
American Indian/Alaskan	1 (5%)
Unknown	1 (5%)
Stage at Entry	
Locally advanced	3 (14%)
Metastatic	17 (77%)
Unknown	2 (9%)
Prior Lines of Treatment	
1-2	9 (41%)
3 or more	13 (59%)

Table 2: Patient Demographics

NCI Protocol 10250_was a single-arm, open-label, multi-center (ETCTN) phase II study to evaluate T + O in patients with advanced uLMS with progression on at least one prior line of systemic treatment. The data presented here represent an analysis performed in April 2021 and were presented as an oral abstract at the American Society of Clinical Oncology (ASCO) Annual Meeting 2021 [11].

The treatment regimen was T 75 mg/m^2 PO daily plus O (tablets) 200 mg PO twice daily days 1-7 of a 21-day cycle based on the RP2D from a phase 1 study in SCLC [13]. The primary endpoint was the confirmed ORR within 6 months of initiating treatment. A one-stage binomial design was used to evaluate for an ORR of at most 10% (null hypothesis) versus at least 35% (alternative hypothesis). The design called for 22 patients, allowing 2-3 additional patients to replace screen failures or patients deemed not evaluable. If 5 or more patients responded, the treatment would be considered worthy of further study. 24 patients were enrolled. One patient did not start treatment due to anemia and another patient discontinued on the first day for ongoing grade 2 colitis from prior treatment with pembrolizumab, resulting in 22 evaluable patients. The characteristics of the patients are shown in Table 2. All patients were female, with a median age of 55 and an ECOG performance status (PS) of 0 or 1. Approximately 60% of patients had received 3 or more prior lines of treatment.

As of April 2021, 4 patients remain on treatment. Reasons for treatment discontinuation were radiographic disease progression (14), clinical disease progression (1) and toxicity (3). 5 patients met the primary endpoint of confirmed objective response within 6 months of starting treatment (5/22, 23%) and the study met the primary endpoint. Best overall response was complete response (0%), partial response (6/22, 27%), stable disease (9/22, 41%), progressive disease (4/22, 18%) and not evaluated (3/22, 14%, all were off for toxicity before first scan). The median PFS for T + O was 6.9

months (95% CI 5.4 months – NE) (**Figure 1**). Median PFS for T + O among patients treated in the third-line setting was 11.0 months (n = 5). An objective reduction in the size of target tumor lesions was observed in 60% of patients (**Figure 2**). Among the 6 patients achieving partial response, the median duration of response was 12.0 months (9.5 months – NE). Responses occurred early in treatment, 3 of 6 patients achieving partial response remain on active therapy and a number of patients achieved prolonged stable disease (**Figure 3**).

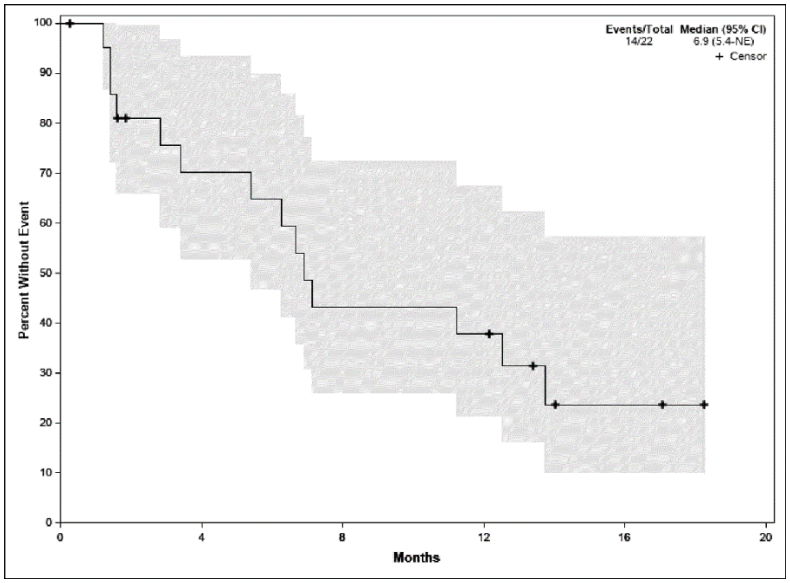


Figure 1: Kaplan-Meir PFS Plot for NCI Protocol 10250

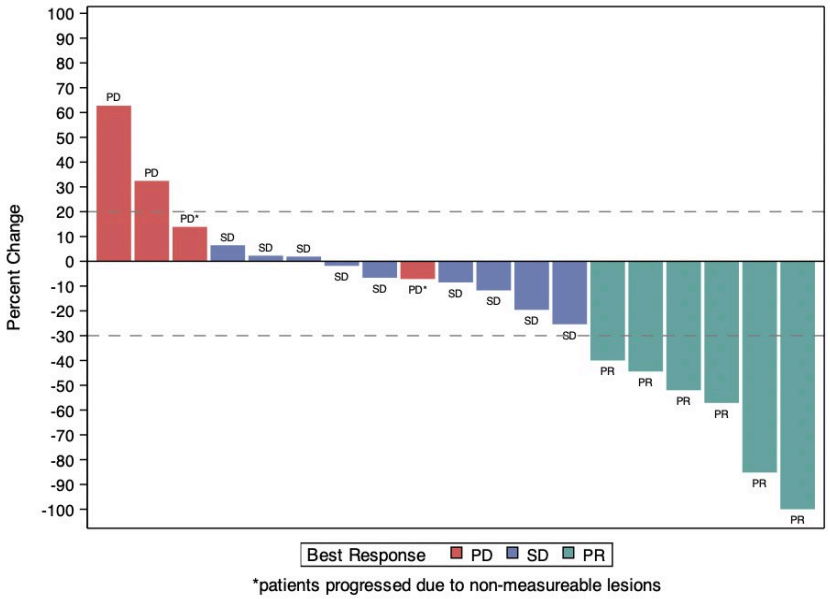


Figure 2: Waterfall Plot/Best Overall Response per RECIST

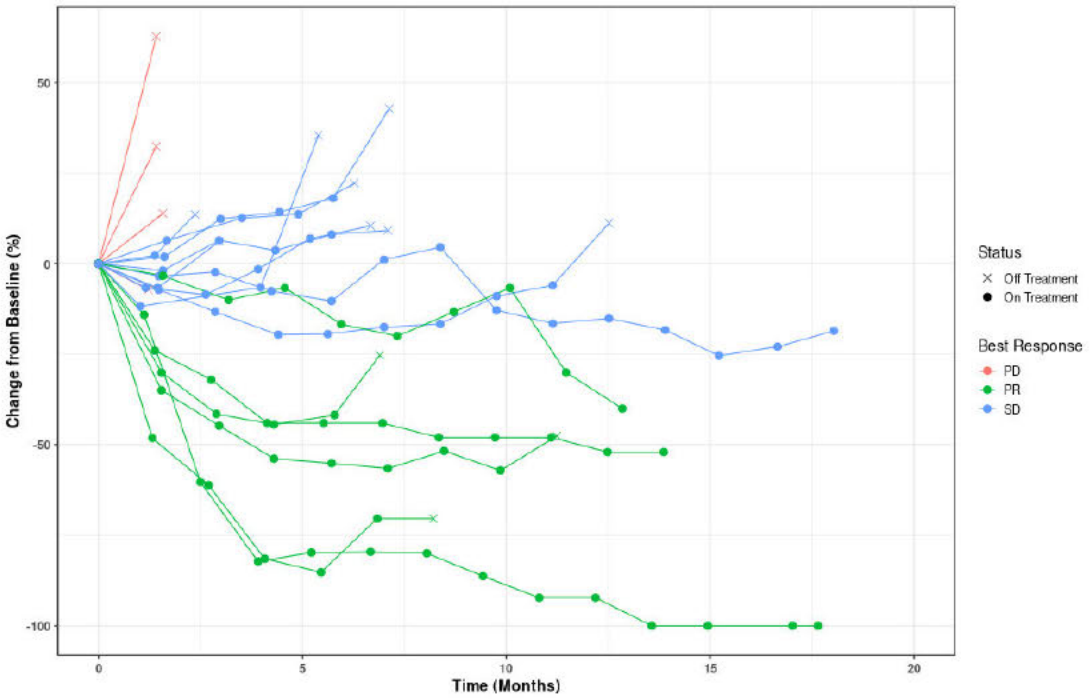


Figure 3: Swimmers Plot Showing RECIST Response By Timepoint

Treatment-emergent treatment-related adverse events are summarized in **Table 3**. Three patients discontinued study participation for adverse events: hematologic toxicity (2) and rash (1). Most AEs associated with study treatment were hematologic. Grade 3/4 neutropenia occurred in 77% of patients and grade 3/4 thrombocytopenia in 32%. However, there were no events of neutropenic fever or thrombocytopenia with bleeding. Dose reduction of T occurred in 55% of patients and dose reduction of O in 45% of patients. Protocol guidelines for management of hematologic toxicity were conservative and required dose reduction if ANC < 1000/uL or platelets < 50,000/uL (regardless of clinical sequelae), reflecting more aggressive management than used in routine clinical practice for T. Dose reduction occurred early and did not appear to affect efficacy. Many of the patients achieving PR underwent dose reduction early in their course of treatment.

Toxicity	All Grade	Grade 3	Grade 4
Neutropenia	90%	59%	18%
Thrombocytopenia	86%	14%	18%
Leukopenia	77%	18%	4%
Anemia	68%	32%	
Fatigue	54%		
Nausea	50%	4%	
Constipation	32%		
Anorexia	27%		
Lymphocytes decreased	27%	9%	
Diarrhea	18%	4%	
Vomiting	18%		
Dry Skin	14%		
Gastroesophageal reflux	14%		
Oral pain	14%		
Rash, maculo-popular	14%	4%	

Table 3: Treatment-Related Toxicity in 10% or More of Patients

Paired tissue biopsies were obtained from all patients participating on NCI 10250. Tissue is being evaluated with several assays intended to measure HR deficiency. These include (a) whole exome sequencing (WES) for genomic alterations in HR pathway genes (b) RAD51 foci formation, a functional biomarker for HR pathway status and (c) SLFN11 expression. In addition, tumors are being evaluated for MGMT expression, because MGMT deficiency is a known predictive biomarker for response to T in other cancer types.

Results of WES are available for a subset of patients (n = 16) with adequate DNA extracted from tumor biopsies. In this analysis, 3 patients who ended treatment for toxicity and did not undergo study-specified restaging imaging (and for whom efficacy cannot therefore be assessed) were excluded. In this analysis, we found one homozygous deletion in RAD51B, one homozygous deletion in PALB2, one deleterious mutation in ATR and two deleterious mutations in ATRX (**Figure 4**). The patients with homozygous deletions of RAD51B and PALB2 were the patients with the longest PFS on study among patients with available WES data (**Figure 4**). However, patients with no detectable genomic alterations in the defined panel of HR pathway genes also experienced objective responses and prolonged PFS. The study team is attempting additional DNA extractions on the remaining patients for whom WES could not be performed during the first analysis.

We also analyzed pre-treatment samples using a RAD51 foci formation assay developed by Shapiro et. al. The RAD51 assay is a functional assessment of HR pathway status. RAD51 assay results are available for 16 patients (for 4 patients, no tissue was available, and for 2 patients, the assay yielded an indeterminate result). We found that, overall, 52% of tumors were HR deficient by the RAD51 assay. Patients with HR deficient tumors by this assay had increased clinical benefit from study treatment. Unfortunately, there were limited samples available from patients with best response of PD or PR. 6 of 12 patients with available pre-treatment samples yielded an HR-deficient result. There appeared to be enrichment of HR-deficiency as measured by this assay among patients with prolonged PFS; however, some patients with objective responses and prolonged PFS were still classified as HR-proficient (**Figure 4**). Of patients with PFS $\geq$ 6 months who had results available from the assay, 7/8 (87%) had HR deficient tumors. Of patients with PFS < 6 months, only 2/8 (25%) were HR deficient. In addition, the median PFS for patients with HR deficient tumors and HR proficient tumors was 342 days versus 56 days, respectively (log rank p = 0.0024).

In an exploratory analysis, we determined HRD scores using WES data from pre-treatment samples and the scarHD algorithm. The HRD score is the sum of telomeric allelic imbalance, loss of heterozygosity and large-scale state transitions and may represent a genomic "scar" reflecting an HR deficient phenotype. HRD scores determined using WES data have been shown to correlate well with traditional SNP-based assays[22]. HRD scores have shown some predictive potential for response to PARPi in ovarian cancer and other contexts. The HRD scores in our uLMS cohort appear elevated (**Figure 4**). Among the 13 patients with HRD score assessed on a pre-treatment biopsy, the median HRD score was 51 (range 36-66) and 10/13 had a score $\geq$ 42. In a TCGA analysis of 33 tumor types, the median HRD score was approximately 20[23]. In studies in ovarian cancer, HRD cutoff scores above 42 were associated with greater likelihood of benefit from PARPi. These findings are suggestive of HR deficiency even in cases without a discernable mutation in an HR pathway gene or a deficient result from the RAD51 foci formation assay. These findings could reflect the high levels of genomic and replicative stress present in uLMS, which could itself impart sensitivity to PARPi in the absence of alterations in HR genes based on emerging research.

Patient	PFS_Time	BOR	Reason Off	RAD51_Pre	Genomics - HR	Genomics - Other	HD (RB/TP53/PTEN/ATRX)
AZ073-0006	8	NE	AE	Proficient			TP53
CA141-0024	37	PD	PD	Proficient			
MA034-0018	43	PD	PD	Proficient		TP53	
NY024-0003	43	PD	PD	Not Done	(Not done: not available)		
MA036-0015	48	PD	PD	Not Done	(Not done: not available)		
PA015-0001	49	NE	AE	Deficient		TP53	
FL015-0017	56	NE	AE	Proficient		MED12	RB, TP53
NY024-0002	86	SD	PD	Proficient	ATRX		RB
VA010-0022	104	SD	PD	Deficient	(Not done: new sample sent)		
FL080-0012	164	SD	PD	Proficient	ATRX	TP53	
MA036-0020	191	SD	PD	N/A	(Not done: new sample sent)		
FL080-0008	203	SD	PD	Deficient		TP53	
MA036-0005	210	PR	PD	Proficient			TP53
MO011-0027	217	SD	PD	Deficient	ATR	CREBPP	
MA036-0025	323	SD		Deficient			
PA015-0026	323	PR		Not Done	(Not done: not available)		
OH007-0016	328	PR		Deficient			RB
MA036-0010	342	PR	PD	Deficient			PTEN
AZ073-0007	348	PR		N/A		TP53	
MA036-0014	381	SD	PD	Deficient	PALB2	TP53, MED12	
FL080-0009	425	PR		Not Done	(Not done: not available)		
FL080-0004	472	SD		Deficient	RAD51B		

MA036-0019	Eligibility violation
MA034-0011	Did not start treatment

	On study as of 4/26/2022

PFS, ORR data are from 2/2021

	Mutation
	Homozygous deletion

Figure 4: Whole-exome sequencing results in HR-gene panel annotated by clinical outcome

We also evaluated SLFN11 and MGMT expression by RNAseq. We did not observe a correlation between SLFN11 or MGMT expression in either the pre-treatment or on-treatment biopsies and clinical outcomes (ORR, PFS) (**Figure 5).** COSMIC signature 3, although present in some samples, also did not appear to predict for clinical benefit.

In summary, a subset of patients deriving greater benefit from olaparib and temozolomide could be identified by WES for HR gene defects and the RAD51 foci formation assay. The RAD51 assay appears particularly promising for selecting patients for treatment with this approach, but limitations include the need for a tissue biopsy prior to treatment and the fact this assay is not currently CLIA certified. Some patients who derived clinical benefit could not be identified by the biomarker analysis used in this study. Overall, results from NCI 10250 are supportive of further development of this treatment approach in a biomarker-unselected population at this time.

Patient	PFS_Time	BOR	Reason Off	SLFN11_Pre	SLFN111_Post	MGMT_Pre	MGMT_Post	Sig3_Pre
AZ073-0006	8	NE	AE	61.80		11.34		0.000
CA141-0024	37	PD	PD	27.76		5.67		0.078
MA034-0018	43	PD	PD		59.74		13.98	
NY024-0003	43	PD	PD					
MA036-0015	48	PD	PD					
PA015-0001	49	NE	AE	33.92		6.94		0.000
FL015-0017	56	NE	AE	12.65		17.50		0.176
NY024-0002	86	SD	PD	29.25	30.47	19.59	30.23	0.000
VA010-0022	104	SD	PD		17.07		14.65	
FL080-0012	164	SD	PD	5.80	19.56	3.54	1.46	0.393
MA036-0020	191	SD	PD	7.05		13.85		
FL080-0008	203	SD	PD	15.37	33.61	30.45	21.09	0.207
MA036-0005	210	PR	PD	11.89	29.09	1.21	8.43	0.260
MO011-0027	217	SD	PD	26.22	24.62	6.41	7.45	0.068
MA036-0025	323	SD		54.23	45.09	11.66	8.93	0.061
PA015-0026	323	PR						
OH007-0016	328	PR		24.32	32.66	4.51	8.40	0.221
MA036-0010	342	PR	PD	41.99	40.46	27.87	16.72	0.000
AZ073-0007	348	PR			32.48		6.82	
MA036-0014	381	SD	PD	22.97	24.08	2.31	4.91	0.000
FL080-0009	425	PR						
FL080-0004	472	SD		2.95	6.22	4.53	6.53	

Figure 5: SLFN11 and MGMT expression by RNAseq

Therefore, on the basis of emerging evidence that uLMS may represent an HR-deficient cancer with high levels of replicative stress, supportive preclinical data and the results of a completed single-arm phase 2 study, we propose to further evaluate temozolomide and olaparib versus investigator's choice for the treatment of patients with advanced uLMS who have progressed on prior chemotherapy.

2.0 OBJECTIVES

2.1 Primary objective

2.1.1 Phase 2 primary objective

To compare the progression free survival (PFS) of olaparib plus temozolomide (Arm 1) as compared to investigator's choice (trabectedin or pazopanib) (Arm 2) for the treatment of patients with advanced uLMS who have received two or more prior lines of therapy as determined by investigator (local site) assessment.

2.1.2 Phase 3 primary objective

To compare the overall survival (OS) of olaparib plus temozolomide (Arm 1) as compared to investigator's choice (trabectedin or pazopanib) (Arm 2) for the treatment of patients with advanced uLMS who have received two or more prior lines of therapy.

2.2 Secondary objectives

2.2.1 (Phase 2/3) To evaluate the safety and tolerability of each treatment by determining adverse events using CTCAE version 5 and patient-reported toxicity using PRO-CTCAE version 1 in and across each treatment arm.

2.2.2 (Phase 2/3) To evaluate the objective response rate (ORR), duration of response (DOR) and disease control rate (DCR) in and across each treatment arm as determined by investigator assessment.

2.3 Exploratory Objective

2.3.1 [redacted]

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

  A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s). Please note that an optional signature line has been provided for use by institutions wishing to use the eligibility checklist as source documentation.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease:**

- Histologically confirmed leiomyosarcoma of uterine origin, as established by the site institutional practice for pathology confirmation for research studies when enrolling the patient on study. Central pathology review will not occur.
- Metastatic or locally advanced and surgically unresectable disease, in the opinion of the treating investigator.

___ **3.2.2 Measurable Disease per RECIST v1.1 (see Section 11.0):** Patients must have at least one lesion that is measurable per RECIST v1.1 criteria to be eligible for the study.

___ **3.2.3 Not Pregnant and Not Nursing,** because this study involves agents that have known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.

___ **3.2.4 Age ≥ 18 years**

___ **3.2.5 ECOG Performance Status ≤ 2** (See Appendix VI)

___ **3.2.6 Prior Treatment**

- Patients must have had prior progression on, or intolerance to, at least two prior lines of systemic therapy for advanced uLMS, one of which was an anthracycline (anthracycline monotherapy or combination). Adjuvant chemotherapy will qualify as a prior line of treatment. Endocrine treatment will not qualify as a prior line of treatment.
- Patients may not have received prior treatment with any PARP inhibitor, temozolomide or dacarbazine (IV analogue of temozolomide).
- Patients may not have had prior treatment with BOTH of the agents included on the investigator's choice arm: trabectedin AND pazopanib. If the patient has had prior treatment with one of these agents, they are eligible; however, they must be assigned to the other agent for investigator's choice. That is, patients who have received prior pazopanib must be assigned to trabectedin, and patients who have received prior trabectedin must be assigned to pazopanib.
- Patients must have recovered to baseline or ≤ grade 1 per CTCAE version 5.0 from toxicity related to any prior treatment, unless adverse events are clinically nonsignificant and/or stable on supportive therapy, with the exception of fatigue (which must be ≤ grade 2), alopecia and/or endocrinopathies related to prior immunotherapy which are controlled with hormone replacement.
- Patients must have completed all prior anti-cancer treatment, including radiation, ≥ 28 days prior to registration.

___ **3.2.7 Prior Surgery**

- Patients may have undergone major surgery (related or unrelated to their cancer diagnosis) ≥ 28 days of registration. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

___ **3.2.8 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1500/mm^3
Platelet count	≥ 100,000/mm^3
Creatinine[1]	≤ 1.5 * ULN
Hemoglobin[2]	≥ 9 g/dL
Total bilirubin[3]	≤ 1.5 x ULN
AST/ALT	≤ 3 x ULN

[1] If creatinine > 1.5 * ULN, CrCl must be > 50 mL/min per Cockcroft-Gault method.

[2] No transfusions ≤ 14 days before C1D1

[3] If documented Gilbert's: ≤ 2.0 x ULN

All criteria are specified with reference to the institution's normal ranges.

___ **3.2.9 Comorbidities – Cardiovascular Conditions**

- Patients may not have uncontrolled hypertension defined as a BP > 150/90 on two consecutive assessments during the screening period. If a patient is found to have a BP > 150/90 on two consecutive assessments during the screening period, the patient may be started on an anti-hypertensive regimen, and will be considered eligible if two subsequent measurements are performed and the BP is ≤ 150/90. If BP is in range on the first measurement, no further measurements are needed.
- Patients must demonstrate a QTcF (Fredericia formula) ≤ 470 msec on an EKG performed during screening. This criterion applies only to patients who will receive pazopanib if randomized to Arm 2 (see Section 3.2.13). Repeat EKG testing during the screening period is allowed.
- Patients may not have an uncontrolled ventricular arrhythmia or recent (within 3 months) myocardial infarction
- In addition to the above, patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (see Appendix VII). To be eligible, patients should be class 2B or better.

___ **3.2.10 Comorbid Comorbidities – Other Conditions**

- **Patients may not have a history of active or unresolved: perforation, abscess or fistula** within 28 days prior to registration (either clinically or radiographically).
- **MDS/AML**: Patients must not have myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or a history of bone marrow biopsy findings at any time consistent with MDS and/or AML.
- **Hepatitis B**: For patients with evidence of chronic hepatitis B (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
- **Hepatitis C:** Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
- **HIV/Immunosuppressive Conditions:** HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

- **Other Malignancies:** Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
- **CNS/Leptomeningeal Disease:** Patients with CNS/leptomeningeal disease must have undergone definitive treatment, have no evidence of CNS progression on follow-up imaging performed at least 4 weeks after the CNS-directed therapy is completed, and be off all steroids, in order to be eligible..
- **Other Medical Conditions:** Patients must not have an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution computed tomography (HRCT) scan or any other condition that would limit compliance with study requirements.
- Patients must be able to swallow oral medications.

___ **3.2.11 Concomitant medications**

- Patients may not require concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks. See Section 8.1.10 for more information.
- Patients may not require concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. See Section 8.1.11 for more information.

___ **3.2.12 Language**

In order to complete the mandatory patient-completed measure, participants must be able to read English or Spanish. Non-English or non-Spanish readers may still participate in the study but are not required to complete the PRO-CTCAE side effect surveys.

___ **3.2.13 Investigator's Choice Arm Assignment and Eligibility**

For all patients, prior to randomization and as part of eligibility, the investigator must select the agent which the patient would receive if assigned to the investigator's choice arm, prior to randomization. The patient must meet all eligibility criteria for that agent during screening and prior to randomization.

Patients without central venous access must be willing to undergo placement of central venous access (i.e. port or PICC line, per institutional practice). if assigned to the investigator's choice arm and if the investigator intends to treat the patient with trabectedin. The site must be able to place central venous access within 10 days of registration/randomization.

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Alliance Patient Number _____

Patient's Initials (L, F, M) _____

Research RN/CRP Signature and Date _____

Physician Signature and Date _____

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- **Investigator (IVR)** — MD, DO, or international equivalent;
- **Non-Physician Investigator (NPIVR)** — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- **Associate Plus (AP)** — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges; and
- **Associate (A)** — other clinical site staff involved in the conduct of NCI-sponsored trials;

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, licensure, and certification)	✓	✓	✓	
GCP Training Certificated (mandatory file upload)	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional file upload)	✓	✓	✓	

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 Additional Site Registration Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on Protocols in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A092104*.
- Click on *Documents, Protocol Related Document*s, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegPref@ctsu.coccg.org to receive further instruction and support.

4.2.4 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks

4.2.5 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application which is accessible via the Delegation Log link on the CTSU members' website

or directly at https://dtl.ctsu.org. 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 to 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 describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.3.2 Patient-reported outcomes

This study includes the use of the mandatory patient completed measures, PRO-CTCAE. The measures are available in English and Spanish. Patients who are able to speak, understand, and read English or Spanish will be required to participate in completing the PRO-CTCAE. For eligible patients that are non-English or non-Spanish readers, they may still participate in this study, but will not complete the PRO-CTCAE surveys.

Patient-reported outcomes for this study will be assessed using paper booklets.

Patient questionnaire booklets

Patient questionnaire booklets are to be downloaded prior to the registration of any patients. The current version of the patient-completed booklets can be downloaded from the CIRB Approved Documents tab of the A092104 page of the CTSU website. Booklets will be provided in English and Spanish (see Section 6.3).

4.3.3 Selecting Study Agent

The investigator must select the agent which the patient will receive if assigned to the investigator's choice arm *prior to randomization* See Section 4.5.

4.4 Patient Enrollment

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;

- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN- related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.5 Stratification Factors and Treatment Assignments

4.5.1 Stratification Factors

1) ECOG PS: 0 or 1 vs. 2
2) Prior lines of treatment: 2 vs. 3 or more

4.5.2 Treatment Assignments

The factors defined in Section 4.5.1 will be used as stratification factors.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure [19] which balances the marginal distributions of the stratification factors between the treatment groups.

The treating physician must determine whether the patient will be treated with either trabectedin or pazopanib (should the patient be assigned to investigator's choice) prior to randomization and this information will be collected prior to randomization. If the patient is assigned to Arm 2, the patient will then initiate treatment with that agent. The drug to which the patient is assigned will be recorded in the eCRFs. The treating investigator will discuss the outcome of the randomization and the treatment assignment with the patient.

1) **Arm 1**: Olaparib + Temozolomide
2) **Arm 2**: Investigator's Choice: Trabectedin or Pazopanib

5.0 STUDY CALENDAR

Pre-study Testing Intervals

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

Study Calendar Key:

"*", "**", "†", etc., are used for additional information relating to the column headers.

"(1)", "(2)", "(3)", are added to the X's for further explanation.

"X"'s are replaced with "A" "B" "C", for tests that vary from the schedule named in the column header.

Study Calendar Arm 1: Olaparib + Temozolomide				
	Prior to Registration*	**Day 1 of Every Cycle****	**Post-treatment follow-up (short-term follow-up)*****	**Long-term follow-up********
Tests & Observations				
H&P, weight, ECOG PS	X(1)	X(1)	X(1)	
Height	X			
Vital signs	X	X	X	
Adverse Event Assessment - CTCAE	X(2)	X(2)	X(2)	
Adverse Event Assessment-PRO-CTCAE	X(2)	X(2)		
Patient medication diary		X(3)		
Survival Follow-up				X
Laboratory Studies				
Complete blood count with differential[7]	X	X	X	
Complete chemistry[8]	X	X	X	
Serum or urine HCG	X(4)			
Staging				
Genomic sequencing results	X(5)			
Imaging (CT or MRI)	X(6)	X(6)	X(6)	
Correlative Studies: For Patients who consent to participate				
A092104 Biobanking	Blood and tissue samples will be collected; see Sections 6.2 and 14.0			

* All screening assessments must be completed ≤ 28 days prior to registration, except for the pregnancy test, which must be completed ≤ 7 days prior to registration. Patients must begin treatment within 14 days after registration/randomization.

** Labs completed prior to registration may be used for C1D1 if obtained ≤ 7 days prior to treatment. For subsequent cycles, all assessments may be obtained within 72 hours (3 days) prior to day of treatment. If there is a change in the patient's clinical status, the assessments should be repeated prior to beginning treatment for that respective cycle. After C1D1, a new treatment cycle may begin ± 3 days from the planned date.

*** Physical examination, adverse event assessment, and medication diary are required 4 weeks (± 7 days) after the end of treatment (defined as the day the investigator determines the patient will not continue study treatment). Patients will then enter long-term follow-up as described below. Patients discontinuing treatment for reasons other than progressive disease will continue following the Study Calendar for disease assessments (i.e. imaging) until progressive disease is documented, and will then enter long-term follow-up.

**** Upon progression, patients will be followed every 3 months (±7 days) for the first 2 years, then every 6 months (±14 days) thereafter until 5 years post-randomization or death, whichever comes first. Information must be collected on (a) the first subsequent anticancer treatment received and (b) survival status. Information may be collected by telephone call or clinical visits conducted as standard of care, per investigator's discretion.

1 A complete physical exam is performed at screening and the post treatment follow-up visit. A limited, symptom based, physical exam is performed at other timepoints.

2 CTCAE must be completed during screening but prior to C1D1, on Day 1 of every cycle, and at the post-treatment follow-up visit. PRO-CTCAE must be completed during screening but prior to C1D1 and on Day 1 of every cycle through cycle 11. Collection of PRO-CTCAE is discontinued after cycle 11. **PRO-CTCAE is required only for English and Spanish readers.**

3 If the sample medication diary in Appendix III and IV is used, it should begin the day the patient starts taking the medication and should be completed and returned to the treating institution on Day 1 of every cycle beginning with Cycle 2. Compliance must be documented by any member of the care team..

4 For women of childbearing potential (see Section 3.2.3). Must be done ≤ 7 days prior to registration.

5 Results from genomic sequencing assays will be collected when known to the treating investigator and previously performed as part of the patient's clinical care. Results from any genomic testing performed on tumor tissue should be reported, including next generation sequencing (extended or targeted panels), whole exome and/or whole genome sequencing. Results will be abstracted and entered into a study-specific form in Medidata by site staff. Copies of deidentified reports from the assay(s) will also be uploaded. Sites must provide this information when available within 60 days of registration.

6 CT scan with IV and oral contrast is recommended to assess disease status. MRI and/or bone scans may be used as clinically indicated per the treating physician's discretion. Imaging is performed every 2 cycles (6 weeks) as measured from C1D1 until disease progression. A window of ±7 days is permitted. Imaging should be performed before a new cycle starts whenever possible.

7 Include white blood cells, absolute neutrophils, hemoglobin, hematocrit and platelets

8 Include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase.

Study Calendar Arm 2: Trabectedin				
	Prior to Registration*	**Day 1 of Every Cycle****	**Post-treatment follow-up (short-term follow-up)*****	**Long-term follow-up********
Tests & Observations				
H&P, weight, ECOG PS	X(1)	X(1)	X(1)	
Height	X			
Vital signs	X	X	X	
Adverse Event Assessment - CTCAE	X(2)	X(2)	X(2)	
Adverse Event Assessment- PRO-CTCAE	X(2)	X(2)		
Survival follow-up				X
Laboratory Studies				
Complete blood count with differential[7]	X	X	X	
Complete chemistry[8]	X	X	X	
CPK[9]		X	X	
Serum or urine HCG	X(3)			
Echocardiogram/MUGA		X(A)		
Staging				
Genomic sequencing results	X(5)			
Imaging (CT or MRI)	X(6)	X(6)	X(6)	
Correlative Studies: For Patients who consent to participate				
A092104 Biobanking	Blood and tissue samples will be collected; see Sections 6.2 and 14.0			

* All screening assessments must be completed ≤ 28 days prior to registration, except for the pregnancy test, which must be completed ≤ 7 days prior to registration, and the baseline MUGA can be obtained up to ≤ 28 days prior to registration. Patients must begin treatment within 14 days after registration/randomization.

** Labs completed prior to registration may be used for C1D1 if obtained ≤ 7 days prior to treatment. For subsequent cycles, all assessments may be obtained within 72 prior to day of treatment. If there is a change in the patient's clinical status, the assessments should be repeated prior to beginning treatment for that respective cycle. After C1D1, a new treatment cycle may begin ± 3 days from the planned date.

*** Physical examination, adverse event assessment, and medication diary are required 4 weeks (± 7 days) after the end of treatment (defined as the day the investigator determines the patient will not be continuing study treatment). Patients will then enter long-term follow-up as described below. Patients discontinuing their treatment for reasons other than progressive disease will continue following the Study Calendar for disease assessments (i.e. imaging) until progressive disease is documented, after which these patients will also enter long-term follow-up.

**** Upon progression, patients will be followed every 3 months (±7 days) for the first 2 years, then every 6 months (±14 days) thereafter until 5 years post-randomization or death, whichever comes

first. Information must be collected on (a) the first subsequent anticancer treatment received and (b) survival status. Information may be collected by telephone call or clinical visits conducted as standard of care, per investigator's discretion.

1 A complete physical exam is performed at screening and the post-treatment follow-up visit. A limited, symptom based, physical exam is performed at other timepoints.

2 CTCAE must be completed during screening but prior to C1D1, on Day 1 of every cycle, and at the post-treatment follow-up visit. PRO-CTCAE must be completed during screening but prior to C1D1 and on Day 1 of every cycle through cycle 11. Collection of PRO-CTCAE is discontinued after cycle 11. **PRO-CTCAE is required only for English and Spanish readers.**

3 For women of childbearing potential (see Section 3.2.3). Must be done ≤ 7 days prior to registration.

4 Results from genomic sequencing assays will be collected when known to the treating investigator and previously performed as part of the patient's clinical care. Results from any genomic testing performed on tumor tissue should be reported, including next generation sequencing (extended or targeted panels), whole exome and/or whole genome sequencing. Results will be abstracted and entered into a study-specific form in Medidata by site staff. Copies of deidentified reports from the assay(s) will also be uploaded. Sites must provide this information when available within 60 days of registration.

5 CT scan with IV and oral contrast is recommended to assess disease status. MRI and/or bone scans may be used as clinically indicated per the treating physician's discretion. Imaging is performed every 2 cycles (6 weeks) as measured from C1D1 until disease progression. A window of ±7 days is permitted. Imaging should be performed before a new cycle starts whenever possible.

6 Include white blood cells, absolute neutrophils, hemoglobin, hematocrit and platelets.

7 Include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase.

8 CPK must be performed and resulted, on day 1 of every cycle prior to treatment with trabectedin.

A Perform transthoracic echocardiography (TTE) or MUGA at baseline (before C1D1 treatment), and while on treatment with trabectedin, as clinically indicated.

Study Calendar Arm 2: Pazopanib				
	Prior to Registration*	**Day 1 of Every Cycle****	**Post-treatment follow-up (short-term follow-up)*****	**Long-term follow-up********
Tests & Observations				
H&P, weight, ECOG PS	X(1)	X(1)	X(1)	
Height	X			
Vital signs	X	X	X	
Adverse Event Assessment - CTCAE	X(2)	X(2)	X(2)	
Adverse Event Assessment- PRO-CTCAE	X(2)	X(2)		
Patient medication diary		X(3)		
Assess for dose escalation		X(4)		
Survival follow-up				X
Laboratory Studies				
Complete blood count with differential[12]	X	X	X	
Complete chemistry[13]	X	X	X	
TSH		X(5)		
Urine spot protein : creatinine ratio (UPC)		X(6)		
Serum or urine HCG	X(7)			
EKG	X(8)			
Echocardiogram/MUGA		X(A)		
Staging				
Genomic sequencing results	X(10)			
Imaging (CT or MRI)	X(11)	X(11)	X(11)	
Correlative Studies: For Patients who consent to participate				
A092104 Biobanking	Blood and tissue. Samples will be collected; see Sections 6.2 and 14.0			

* All screening assessments must be completed ≤ 28 days prior to registration, except for the pregnancy test, which must be completed ≤ 7 days prior to registration. The MUGA can be obtained up to ≤ 28 days prior to registration. Patients must begin treatment within 14 days after registration/randomization.

** Labs completed prior to registration may be used for C1D1 if obtained ≤ 7 days prior to treatment. For subsequent cycles, all assessments may be obtained within 72 prior to day of treatment. If there is a change in the patient's clinical status, the assessments should be repeated prior to beginning treatment for that respective cycle.

*** Physical examination, adverse event assessment, and medication diary are required 4 weeks (± 7 days) after the end of treatment (defined as the day the investigator determines the patient will not be continuing study treatment). Patients will then enter long-term follow-up as described below. Patients

discontinuing their treatment for reasons other than progressive disease will continue following the Study Calendar for disease assessments (i.e. imaging) until progressive disease is documented, after which these patients will also enter long-term follow-up.

**** Upon progression, patients will be followed every 3 months (±7 days) for the first 2 years, then every 6 months (±14 days) thereafter until 5 years post-randomization or death, whichever comes first. Information must be collected on (a) the first subsequent anticancer treatment received and (b) survival status. Information may be collected by telephone call or clinical visits conducted as standard of care, per investigator's discretion.

1 A complete physical exam is performed at screening and the post-treatment follow-up visit. A limited, symptom based, physical exam is performed at other timepoints.

2 CTCAE must be completed during screening but prior to C1D1, on Day 1 of every cycle, and at the post-treatment follow-up visit. PRO-CTCAE must be completed during screening but prior to C1D1 and on Day 1 of every cycle through cycle 11. Collection of PRO-CTCAE is discontinued after cycle 11. **PRO-CTCAE is required only for English and Spanish readers.**

3 If the sample medication diary in Appendix V is used, it should begin the day the patient starts taking the medication and should be completed and returned to the treating institution on Day 1 of every cycle beginning with Cycle 2. Compliance must be documented by any member of the care team..

4 Pazopanib will be initiated at 400 or 600 mg per day per the treating investigator's discretion. Pazopanib can be dose escalated in 200 mg increments to a maximum dose of 800 mg per day at day 1 visits, or earlier intervals, per usual clinical practice. Pazopanib can be dose de-escalated.

5 TSH should be measured as clinically indicated during treatment with pazopanib.

Testing should be performed after registration and once every other cycle (i.e. screening, C2D1, C4D1, …) or more frequently as clinically indicated.

6. UPC should be measured as clinically indicated during treatment with pazopanib. See Section 8 for management of abnormal UPC occurring while on treatment.

7 For women of childbearing potential (see Section 3.2.3). Must be done ≤ 7 days prior to registration.

8 For patients randomized to Arm 2 and treated with pazopanib an EKG should be performed after registration and prior to treatment start if they have a history of or signs/symptoms of dysrhythmias or prolonged QT syndrome or relevant preexisting cardiac disease, and/or on medication for dysrhythmias, and/or electrolyte imbalances that could promote dysrhythmias or to prolong the QT interval. During treatment EKG monitoring, including serum electrolytes (e.g., calcium, magnesium) is per clinical discretion as clinically indicated.

9 Results from genomic sequencing assays will be collected when known to the treating investigator and previously performed as part of the patient's clinical care. Results from any genomic testing performed on tumor tissue should be reported, including next generation sequencing (extended or targeted panels), whole exome and/or whole genome sequencing. Results will be abstracted and entered into a study-specific form in Medidata by site staff. Copies of deidentified reports from the assay(s) will also be uploaded. Sites must provide this information when available within 60 days of registration.

10 CT scan with IV and oral contrast is recommended to assess disease status. MRI and/or bone scans may be used as clinically indicated per the treating physician's discretion. Imaging is performed every 2 cycles (6 weeks) as measured from C1D1 until disease progression. A window of ±7 days is permitted. Imaging should be performed before a new cycle starts whenever possible.

11 Include white blood cells, absolute neutrophils, hemoglobin, hematocrit and platelets.

12 Include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase.

A Perform transthoracic echocardiography (TTE) or MUGA at baseline (before C1D1 treatment), and while on treatment with pazopanib, as clinically indicated.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is the 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; 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 or Rave SLA role must have at a minimum an Associate (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 the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; 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 replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located

on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management > Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

6.1.3 Data Quality Portal

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

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

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for screening, on study, response and progression. Supporting documentation will include radiology reports, pathology reports and clinical notes. These must be submitted at the following time points:

Screening: Pathology report

On-Study: Clinic note, radiology report of the screening/baseline scan, pathology report and tumor genomics (see immediately below).

This study will collect results of genomic testing conducted on tumor tissue which was previously performed as part of the patient's clinical care and for which results are known to the treating investigator at the time of registration. Relevant information includes tumor genomics obtain using next generating sequencing (targeted or extended panels), whole exome and/or whole genome sequencing from in-house platforms or commercial entities (i.e. Foundation Medicine, Caris). Only testing on tumor tissue will be collected. Results from testing on peripheral blood or other sources will not be collected. Relevant data will be abstracted and entered into a study-specific form. Sites will also upload deidentified result reports from the assays. This information must be provided within 60 days of registration.

Partial or Complete Response – Radiology report.

Progression: Radiology report and clinic note for patients deemed to have progression based on clinical deterioration.

Supporting documentation is to be submitted via Rave.

6.1.5 Rave-CTEP-AERS integration

See Section 9.1.1 for information regarding submission of adverse event information utilizing the Rave-CTEP-AERS integration.

6.2 Specimen collection and submission

The Alliance A092104 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

For patients consenting to A092104 Biobanking: All participating institutions must ask patients for their consent to participate in biobanking for future research, although patient participation is optional. For patients who consent to participate, tissue and blood will be collected at the following time points for biobanking. Please also see the study CSM for more instructions regarding specimen collection and submission.

6.2.1 Overview of Specimen Requirements

	Within 60 days of registration	Prior to C1D1	C2D1 (Prior to treatment)	C5D1 (Prior to treatment)	Progression/ End of Treatment
	For patients registered to A092104 biobanking, submit the following:				
Archival FFPE tumor tissue	X				
Plasma and buffy coat from whole blood in EDTA tubes[1]		2 x 10 mL	2 x 10 mL	2 x 10 mL	2 x 10 mL

1. Buffy coat is required only at one timepoint; preferred at Prior to C1D1, but any later timepoint is acceptable.

6.3 Submission of Patient Completed Measures

Patient completed measures will be performed using paper questionnaire booklets.

Patient-completed questionnaire booklets for this study are to be downloaded prior to the registration of any patients (see Section 4.3.2, Patient-reported outcomes). Booklets must be given to patients to complete and patients should be instructed to return the booklets/responses to site staff in person, by mail, or by phone) and site staff will enter patient responses into Medidata Rave. The method of administration (in person, by mail, etc.) should be documented in the source documents. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. The method of collection should be documented in Rave.

Please note that PRO-CTCAE is required for all patients if they are English and Spanish readers per the study calendar.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

6.3.1 Patient Language Considerations

The PRO-CTCAE are available in English and Spanish and are required only for English and Spanish readers. Participation in Alliance A092104 is not restricted to patients who are able to read and understand these languages. The translated measures are available on the A092104 CTSU and Alliance study pages. Ad-hoc translation of patient-completed measures is not permitted.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin within 14 days from the date of study of registration.

For questions regarding treatment, please see the study contacts page.

Please see the study calendar for allowable windows in which treatment cycles must begin. In addition, patients are permitted to have a new cycle of treatment delayed for up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this delay being considered a protocol violation. Documentation to justify this delay should be provided.

70 patients will be enrolled to the Phase II portion of the trial. Enrollment will be paused at that time for treatment evaluation (see Section 13.2.2)

7.1 Arm 1 (Olaparib + Temozolomide)

Patients assigned to Arm 1 will receive treatment with olaparib plus temozolomide.

Temozolomide (TMZ) is administered at 75 mg/m^2 orally once daily in combination with olaparib (tablets) 200 mg orally twice daily on days 1-7 of a 21-day cycle.

Please see below for additional instructions on how to administer this regimen.

Regimen Description					
Agent	***Premedications Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Olaparib	Do not consume grapefruit juice. Take concurrently with TMZ. See Section 8.	200 mg	PO **twice** daily	Days 1-7	21 days (3 weeks)
Temozolomide	Ondansetron 8 mg PO once prior to TMZ (required during cycle #1, optional thereafter). TMZ can be taken with or without food but it may be better tolerated if taken on an empty stomach. Take TMZ with a full glass of water with the AM dose of olaparib; or if nausea is a difficulty, take TMZ with or without food with the PM dose of olaparib	75 mg/m^2 See below for dose table.	PO **once** daily	Days 1-7	

Regimen Description					
Agent	***Premedications Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
	Recommend consistency daily regarding with or without food and regarding AM or PM dosing See Section 8.				

The dose and schedule for temozolomide and olaparib reflect the recommended phase 2 dose (RP2D) from a phase 1 study with this combination in small cell lung cancer. The same RP2D was also determined in a phase 1 clinical trial of this combination in Ewing sarcoma (NCT01858168; unpublished, study team's communication with study PI) and is currently being used in an ongoing phase II study in neuroendocrine tumors (NCT04394858).

Furthermore, this dose and schedule were used in our completed phase 2 study. Hematologic toxicity was the most commonly reported adverse event and included grade 3/4 neutropenia (59%, 18%), thrombocytopenia (15%, 18%) and anemia (32%, 0%). Protocol-mandated dose reductions for temozolomide were made in 54% of patients. Clinically significant complications of myelosuppression, including febrile neutropenia or thrombocytopenia with bleeding, were not observed.

Temozolomide:

Patients will be administered TMZ once daily (QD). The TMZ capsules should be swallowed whole with a glass of water and not opened, crushed, chewed, or dissolved. TMZ can be taken with or without food, but if there are issues with nausea, fasting is recommended (should be taken on an empty stomach [i.e. in the fasted state, either 1 hour before, or 2 hours after, a meal]). Patients should take ondansetron 8 mg PO once concurrently or up to 30 minutes before the TMZ dose during cycle 1. If vomiting occurs, do not repeat dose, patients should wait until next scheduled dose.

If patients have a medical contraindication to ondansetron, another anti-emetic may be substituted. The use of ondansetron beyond cycle 1 is at the discretion of the principal investigator.

TMZ is rapidly and completely absorbed after oral administration with a peak plasma concentration achieved in a median of 1 hour. Food reduces the extent of TMZ absorption. Should any patient enrolled on the study miss a scheduled dose of temozolomide for any reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient should not repeat dose if vomiting occurs after dose is administered; and should wait until the next scheduled dose.

Temozolomide doses are calculated based on body surface area (BSA). Temozolomide doses should be adjusted if a patient's weight changes >10% or more from the baseline (screening) weight. The total daily dose of temozolomide (75 mg/m2) based on patient BSA and the recommended combination of temozolomide capsule strengths to achieve this dose is provided in the tables below. In the event the patient's dose of temozolomide is modified while on the

study, re-calculate the total daily dose, and round off the resulting dose to the nearest 5 mg increment.

Total Daily Dose of TMZ (75 mg/m2) Based on BSA	
BSA (m^2)	75 mg/m2 (mg daily)
1.0	75
1.1	82.5
1.2	90
1.3	97.5
1.4	105
1.5	112.5
1.6	120
1.7	127.5
1.8	135
1.9	142.5
2.0	150
2.1	157.5
2.2	165
2.3	172.5
2.4	180
2.5	187.5

Number of Daily Capsules by Strength (mg) to Achieve Daily Dose					
Total Daily Dose (mg)	180 mg	140 mg	100 mg	20 mg	5 mg
75	0	0	0	3	3
82.5	0	0	0	4	0
90	0	0	0	4	2
97.5	0	0	1	0	0
105	0	0	1	0	1
112.5	0	0	1	0	2
120	0	0	1	1	0

127.5	0	0	1	1	1
135	0	0	1	1	3
142.5	0	1	0	0	0
150	0	1	0	0	2
157.5	0	1	0	1	0
165	0	1	0	1	1
172.5	0	1	0	1	2
180	1	0	0	0	0
187.5	1	0	0	0	1

Olaparib:

Patients will be administered olaparib twice daily (BID). Olaparib tablets should be taken at the same time each day approximately 12 hours apart with one glass of water. The first olaparib dose of the day should be taken concomitantly with TMZ. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food; however, since the morning dose is taken with TMZ, both agents should be taken together on an empty stomach for the morning dose. If taken with or without food, it should consistently be taken in that manner. It is prohibited to consume grapefruit, grapefruit juice, or Seville oranges while on olaparib therapy.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose of olaparib for any reason (e.g., as a result of forgetting to take the tablets or vomiting the tablets), the patient will be allowed to take the scheduled dose of olaparib up to a maximum of 2 hours after the scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose of olaparib is not to be taken and the patient should take the next dose at the next scheduled time.

7.2 Arm 2 (Investigator's Choice: Trabectedin or Pazopanib)

Patients randomized to Arm 2 may be treated with investigator's choice of either trabectedin or pazopanib. **If the patient is randomized to Arm 2, the treating investigator will decide whether the patient will receive treatment with trabectedin or pazopanib. The patient must have previously met all eligibility criteria for the drug to which they are assigned.**

Crossover from trabectedin or pazopanib to olaparib and temozolomide is not permitted.

Trabectedin

Trabectedin will be administered at the FDA-approved dose and schedule: 1.5 mg/m^2 continuous intravenous infusion through a central venous line over 24 hours. Trabectedin must be administered through a central line and cannot be infused peripherally. Dexamethasone 20 mg IV is administered approximately 30 minutes prior to beginning the trabectedin infusion. In subsequent cycles after cycle 1, the dexamethasone dose can be lowered at the investigator's discretion per institutional guidelines/practice.

Trabectedin doses are calculated based on body surface area (BSA). Institutional practice may be followed in determining the trabectedin dose for a given patient. Trabectedin doses should be adjusted if a patient's weight changes >10% or more from the baseline (screening) weight.

Growth factor must be administered with trabectedin. Institutional practice can be followed with regard to the type of growth factor administered. A recommended approach is to use the pegfilgrastim delivery kit which may be applied when the patient returns to disconnect the trabectedin infusion.

Regimen Description					
Agent	***Premedications Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Trabectedin	Dexamethasone 20 mg IV approximately 30 minutes prior to infusion. Appropriate antiemetics (for moderate emetogenic potential) per institutional practice. Administer growth factor (GCSF or GMCSF) following the trabectedin infusion (see Section 8.1.7)	1.5 mg/m^2	Continuous IV infusion over 24 hours on Day 1 through a central venous line (peripheral administration is not permitted).	Day 1	21 days (3 weeks)

Pazopanib

Pazopanib will be administered orally once every day. The FDA approved dose and schedule of pazopanib is 800 mg once daily continuously. However, 800 mg daily is not tolerable for many patients, and most sarcoma medical oncologists initiate treatment with pazopanib at a lower dose and escalate to 800 mg if tolerated.

The most recent randomized clinical trial employing pazopanib (Alliance A091304: a randomized phase 2 trial of MLN0128 versus pazopanib) was interrupted and amended to change the starting dose of pazopanib from 800 mg to 400 mg because of intolerable toxicity on the pazopanib arm where the drug was administered at 800 mg daily to all patients. In the amended version of A091304, investigators were allowed to escalate the dose of pazopanib from the starting dose of 400 mg in 200 mg increments (separated by a minimum of two-week intervals) to a maximum of 800 mg if the drug was well tolerated and at the discretion of the treating investigator.

We will use a similar approach in this study. **Patients may start pazopanib at either 400 mg or 600 mg daily per the treating investigator's discretion.** Patients will be assessed at the day 1 visit of every cycle and may escalate in 200 mg intervals to a maximum of 800 mg daily at the discretion of the treating investigator. Patients may be assessed at an earlier timepoint, and

the dose escalated an earlier timepoint, at the investigator's discretion, per usual standard of care. Dose de-escalation is also allowed per the treating investigator's discretion.

Patients should take pazopanib on an empty stomach either 1 hour before or 2 hours after food. The tablets should be swallowed whole and cannot be crushed or broken. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Regimen Description					
Agent	***Premedications Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Pazopanib	None See Section 8	Initiate at 400-600 mg daily; may increase in 200 mg increments to maximum of 800 mg (see above).	Orally	Daily, continuously	21 days (3 weeks)

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment which would be considered treatment for leiomyosarcoma or impact the primary endpoint. This includes any surgical intervention, non-palliative radiotherapy, any radiotherapy to target lesions, or other local intervention directed at the primary neoplasm or sites of metastatic disease.

8.1.2 **Patients should receive full supportive care while on this study.** This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 **Treatment with hormones or other chemotherapeutic agents may not be administered** except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic**.**

8.1.4 **Antiemetics may be used** at the discretion of the treating investigator, to manage treatment or disease-related nausea and vomiting. Specific anti-emetics will be administered prior to temozolomide and trabectedin, as described in Section 7.0.

8.1.5 **Diarrhea management** is per the discretion of the treating investigator. Diarrhea is a common side effect of olaparib and pazopanib. Diarrhea can be managed conservatively with medications such as loperamide. Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances. If infection is suspected, the appropriate testing should be performed.

8.1.6 **Care of patients with a history of HIV, Hepatitis C, and Hepatitis B**

For eligible patients with a history of chronic HBV infection (whether on suppressive therapy or not) or HCV infection (either treated and cured or on treatment), new or progressive elevation in ALT levels while on study treatment should prompt measurement of HBV or HCV RNA levels. If the patient is found with detectable HBV or HCV RNA,

the patient should be referred to a hepatologist and managed per standard of care for the hepatitis infection. If a change in medical therapy for HBV or HCV is indicated and would result in the use of a prohibited medication as otherwise defined in this section, then the patient should be removed from the study.

For eligible patients with HIV infection, clinical parameters related to the HIV infection, including lymphocyte subset counts and HIV RNA levels, should be monitored by the patient's infectious disease physician per standard of care. Should unfavorable changes occur and a change in medical therapy is indicated which would result in the use of a prohibited medication as otherwise defined in this section, then the patient should be removed from the study.

8.1.7 Palliative radiation therapy may not be administered to patients enrolled on this study.

8.1.8 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating investigator. The treating investigator should carefully consider the risk/benefit ratio before initiating such treatment.

Filgrastim (G-CSF) tbo-filgrastim, and sargramostim (GM-CSF) are permitted at the discretion of the treating investigator. Use of growth factor support is required for patients receiving trabectedin. Their use must be documented and reported.

8.1.9 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions per institutional standards.

8.1.10 CYP3A4 Inhibitors

Chronic concomitant treatment with strong or moderate inhibitors of CYP3A4 is not allowed on this trial. The following drugs are EXAMPLES of strong or moderate inhibitors of CYP3A4 and are not allowed during treatment on any of the study arms (temozolomide/olaparib, trabectedin and pazopanib).

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.11 CYP3A4 Inducers

Chronic concomitant treatment with strong or moderate inducers of CYP3A4 is not allowed on this trial. The following drugs are EXAMPLES of strong or moderate inducers of CYP3A4 and are not allowed during treatment on any of the study arms (temozolomide/olaparib, trabectedin and pazopanib)

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.12 P-gp Inhibitors

It is possible that co-administration of P-gp inhibitors (*e.g.*, amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be exercised when using these agents for patients assigned to temozolomide/olaparib.

8.1.13 Other Drug-Drug Interactions

Olaparib

Medication/Class of Drug	Precautions/Notes
• **CYP3A4 substrates:** hormonal contraceptives, simvastatin, cisapride, cyclosporine, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • **CYP2B6 substrates:** buproprion, efavirinez • **OATP1B1 substrates:** bosentan, glibenclamide, repaglinide, statins and valsartan • **OCT1, MATE1 and MATE2K substrates:** metformin • **OCT2 substrates:** serum creatinine • **OCT3 substrates:** furosemide, methotrexate	Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OCT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP2B6. Caution should be used if substates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that the international normalized ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

Pazopanib

Concomitant use of pazopanib with other agents with narrow therapeutic windows that are metabolized by CYP26 or CYP2C8 is not recommended. Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring. Simvastatin, and other statins, should be discontinued prior to starting pazopanib whenever possible.

8.1.14 Dietary Restrictions and Over-the-Counter/Self-Medication

It is prohibited to consume grapefruit, grapefruit juice, Seville oranges, or Seville orange juice while on olaparib therapy. The use of any natural/herbal products or other traditional remedies should be discouraged for all patients.

8.2 Dose Modifications

8.2.1 Dose Modifications for Olaparib and Temozolomide

The following general guidelines apply to dose reductions and delays:

Dosing for a given cycle will be based on adverse events observed during the prior cycle. When multiple adverse events occur, the modification that would require the patient to receive the lowest dose combination should be used.

When toxicity requires a new treatment cycle to be delayed, both olaparib and temozolomide should be held until the toxicity resolves and then both drugs resumed simultaneously.

If toxicity requires olaparib or temozolomide to be held during the dosing phase (days 1-7) of a cycle, then, in general, both agents should be interrupted, and, in general, treatment should resume at the time of the next scheduled cycle (i.e. the missed doses should not be made up). Deviations from this approach can be discussed with the study chair. When an adverse event results in a study agent(s) being interrupted during a cycle, all planned assessments for that cycle will occur as scheduled. When treatment is interrupted during a dosing cycle due to toxicity, the agent to which toxicity is attributed should be dose-reduced by one level at the time treatment is resumed.

A subject may incur up to 2 dose reductions of both olaparib and temozolomide prior to discontinuation of that agent. Temozolomide may not be dose reduced below 25 mg/m2 daily and olaparib may not be dose reduced below 100 mg BID; in the event reduction below these dose levels is indicated, that study agent should be discontinued. However, after discontinuation of one study agent, the other study agent may be continued at the discretion of the treating investigator.

For adverse events that have not resolved at the scheduled start of a cycle per "Criteria to Begin a New Cycle" immediately below, treatment may be delayed for up to 3 weeks. If, after a 3-week delay, the adverse events have still not resolved, the patient should be removed from the study.

AERS reporting may be required for some adverse events (See Section 9.0).

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

Criteria to Begin a New Cycle

A new cycle of therapy may begin only if each of the following criteria are met:

Parameter	Value
ANC	≥ 1,500/μL
Hemoglobin	≥ 8 g/dL
Platelets	≥ 100,000/μL
Total bilirubin	≤ 2* ULN

AST and ALT	≤ 3* ULN
Non-hematologic toxicity	Grade ≥ 2 non-hematologic adverse events (except for alopecia) have resolved to grade ≤ 1, acceptable grade 2 (in the opinion of the treating investigator), or baseline.

Dose Levels

The following dose levels apply to olaparib and temozolomide.

Note: Olaparib and temozolomide may be dose modified independently.

Dose Level	**Olaparib** **TWICE A DAY x 7 days q21days**	**Temozolomide** **DAILY x 7 days q21days**
Initial Dose	200 mg PO BID	75 mg/m^2 PO daily
Dose reduction 1	150 mg PO BID	50 mg/m^2 PO daily
Dose reduction 2	100 mg PO BID	25 mg/m^2 PO daily

Management of Hematologic Toxicity

Observed Toxicity	Recommended Management for Agent to Which Toxicity is Attributed See also instructions below this table
ANC < 1000/μL Platelets < 50,000/μL Grade 3 or 4 neutropenic fever Grade 3 thrombocytopenia with bleeding Hemoglobin < 7 g/dL Other hematologic adverse events ≥ grade 3 deemed clinically significant by the treating investigator.	Delay cycle. Monitor complete blood count at least weekly. When criteria for new cycle are met, resume at one dose level lower for the agent to which toxicity is assessed.
ANC 1000-1499/μL Platelets 50,000/mcL - 99,999/mcL Hemoglobin < 8 g/dL	Delay cycle. Monitor complete blood count at least weekly. When criteria for new cycle are met, resume treatment at same dose level. If a treatment delay of more than 7 days is required, then, when criteria for the new cycle are met, resume at one dose level lower for the agent to which toxicity is assessed.

Both temozolomide and olaparib are associated with myelosuppression. **In the event of hematologic toxicity requiring dose modification, the investigator should modify the dose of the agent to which the toxicity is attributed. In general, dose modification of temozolomide is appropriate for initial events of neutropenia, thrombocytopenia and anemia. If the investigator is uncertain to which agent toxicity is attributable and recurrent events occur, a stepwise alternating approach in which temozolomide is modified first, followed by olaparib, and so on, can be used.** If guidance is needed, the treating investigator should contact the Study Chair.

Should any subject develop evidence of severe and prolonged hematologic toxicity, including but not limited to ≥2 week interruption/delay in study drug administration due to any of the following, additional monitoring is indicated:

- grade 3 anemia (Hgb <8 g/dL)
- grade 3 neutropenia (ANC <1000/mcL)
- grade 3 thrombocytopenia (platelets <50/mcL) and/or
- development of transfusion dependence for red blood cells or platelets

In any of these cases, weekly blood counts including reticulocytes and peripheral smear, should be monitored. If toxicity has not resolved to ≤ grade 1 within 3 weeks of study drug treatment being held, the patient should be referred to a hematologist for further evaluation and the patient should be removed from the study. Bone marrow biopsy should be considered for evaluation including cytogenetics. Patients who develop MDS or AML while on study treatment should discontinue study participation and be managed appropriately by a hematologist.

Management of Non-Hematologic Toxicity Attributed to Olaparib

Diarrhea Related to Olaparib	Recommended Management
Grade 1	Continue treatment.
Grade 2	Continue treatment. Evaluate for infectious etiology if clinically indicated. Institute anti-diarrheal therapy with loperamide. If diarrhea persists ≥ grade 2 for > 5 days despite supportive care, interrupt olaparib or delay cycle (as appropriate) and manage supportively. Reinstitute at same dose when symptoms improve to ≤ grade 1. Recurrent grade 2 diarrhea: Interrupt olaparib or delay cycle (as appropriate). Evaluate for infectious etiology. Manage supportively. Upon resolution to ≤ grade 1, resume at one dose level lower for olaparib.
Grade 3, and/or treatment interrupted due to adverse event.	Interrupt olaparib or delay cycle (as appropriate) until ≤ grade 1. Evaluate for infectious etiology if clinically indicated. Institute anti-diarrheal therapy. Resume at one dose level lower for olaparib when symptoms improve to ≤ grade 1.
Grade 4	Discontinue olaparib permanently.

Other Non-Hematologic Toxicity Attributed to Olaparib	Recommended Management
Grade 1 or 2	No change in dose. Continue treatment at the investigator's discretion, or interrupt treatment for clinically significant toxicity. For second and subsequent clinically significant grade 2 non-hematologic adverse events attributed to olaparib, dose-reduce olaparib by one dose level.

Other Non-Hematologic Toxicity Attributed to Olaparib	Recommended Management
Grade 3 non-hematologic toxicity deemed clinically significant by the treating investigator, and/or treatment interrupted due to adverse event, and not attributable to TMZ or underlying disease	Interrupt olaparib or delay cycle (as appropriate) until event resolved to grade ≤ 1, acceptable grade 2 (in the opinion of the treating investigator), or baseline. Then resume at one dose level lower for olaparib.
Grade 4 non-hematologic toxicity not attributable to TMZ or underlying disease (except for grade 4 alopecia, fatigue, nausea and vomiting not maximally managed with supportive care)	Discontinue olaparib permanently.

Management of Non-Hematologic Toxicity Attributed to Temozolomide

Non-Hematologic Toxicity Attributed to TMZ	Recommended Management
Intolerable grade 2 toxicity	Interrupt TMZ or delay cycle (as appropriate) until resolved to grade 1, or deemed tolerable with supportive care, then resume at the same dose level.
Grade 3/4 fatigue, nausea, constipation and/or diarrhea which persist > 3 days despite optimal supportive care Other grade 3 adverse event deemed clinically significant by the treating investigator, and/or treatment interrupted due to adverse event.	Interrupt TMZ or delay cycle (as appropriate) until event resolved to grade 1, acceptable grade 2 (in the opinion of the treating investigator), or baseline. Then resume at one lower dose level for TMZ.
Grade 4 (except for grade 4 alopecia, fatigue,	Discontinue TMZ permanently.

nausea and vomiting not maximally managed with supportive care)	

8.2.2 Dose Modifications for Trabectedin

The following general guidelines apply to dose reductions and delays for trabectedin:

Dosing for a given cycle will be based on adverse events observed during the prior cycle. When multiple adverse events occur, the modification that would require the patient to receive the lowest dose of trabectedin is used.

A subject may incur up to 2 dose reductions of trabectedin; in the event that dose reduction below 1 mg/m2 is indicated, trabectedin should be discontinued.

For adverse events that have not resolved at the scheduled start of a cycle per "Criteria to Begin a New Cycle" immediately below, treatment may be delayed for up to 3 weeks. If, after a 3 week delay, the adverse events have still not resolved, the patient should be removed from the study.

Management guidelines for dose modification of trabectedin are consistent with guidelines from the FDA label where available. Investigators may also consult the FDA label/package insert prescribing information for trabectedin.

Patients may not undergo dose re-escalation of trabectedin after dose reduction, consistent with the package insert.

AERS reporting may be required for some adverse events (See Section 9.0).

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

Criteria to Begin a New Cycle

A new cycle of therapy may begin only if each of the following criteria are met:

Parameter	Value
ANC	≥ 1,500/µL
Hemoglobin	≥ 8 g/dL
Platelets	≥ 100,000/µL
Total bilirubin	≤ 1.5 x ULN
AST and ALT	≤ 2.5 x ULN
CPK	≤ 2.5 x ULN
Non-hematologic toxicity	Grade ≥ 3 non-hematologic adverse events (except for alopecia) have resolved to grade ≤ 1, or acceptable grade 2 (in the opinion of the treating investigator), or baseline.

Dose Levels

Dose Level	Trabectedin
Initial Dose	1.5 mg/m^2

Dose reduction 1	1.2 mg/m^2
Dose reduction 2	1 mg/m^2

Management of Hematologic Toxicity

Observed Toxicity	Recommended Management
ANC < 500/µL for > 5 days Platelets < 25,000/µL Grade 3 or 4 neutropenic fever Grade 3 thrombocytopenia with bleeding Hemoglobin < 7 g/dL Other hematologic adverse events ≥ grade 3 deemed clinically significant by the treating investigator.	Delay cycle. Monitor complete blood count at least weekly. When criteria for new cycle are met, resume at one dose level lower for trabectedin.
ANC < 500/µL for ≤ 5 days ANC 500-1499/µL Platelets 25,000/mcL - 99,999/mcL Hemoglobin < 8 g/dL	Delay cycle. Monitor complete blood count at least weekly. When criteria for new cycle are met, resume treatment at same dose level.

Management of Non-Hematologic Toxicity

Observed Toxicity	Recommended Management
Total bilirubin > 2 * ULN and AST or ALT > 3 * ULN Clinical rhabdomyolysis	Permanently discontinue trabectedin.
Total bilirubin > 1.5 * ULN AST/ALT > 5 * ULN Alkaline phosphatase > 2.5 * ULN CPK > 5 * ULN without clinical symptoms of rhabdomyolysis	Delay cycle. Monitor labs at least weekly. When criteria for new cycle are met, resume at one dose level lower.
AST/ALT > 2.5 * ULN but ≤ 5 * ULN CPK > 2.5 * ULN but ≤ 5 * ULN	Delay cycle. Monitor labs at least weekly. When criteria for new cycle are met, resume treatment at same dose level.
Absolute decrease in left ventricular ejection fraction of 10% or more from baseline (screening echocardiogram or MUGA) and less than lower limit of normal, or clinical evidence of cardiomyopathy or heart failure.	Delay cycle. Refer to cardiology. If clinical symptoms resolve and left ventricular ejection fraction improves to within the normal range, resume treatment at one dose level lower at the investigator's discretion.
Grade 3 toxicity not otherwise specified	Delay cycle. When improved to baseline, grade 1 or tolerable grade 2, resume treatment at one dose level lower, except for grade 3 fatigue, nausea or vomiting lasting < 5 days with supportive care, in which case patient may resume at the same dose level.
Grade 4 (except for grade 4 alopecia, fatigue, nausea and vomiting not maximally managed with supportive care)	Discontinue trabectedin permanently.

8.2.3 Dose Modifications for Pazopanib

The following general guidelines apply to dose reductions and delays for pazopanib:

Pazopanib will be initiated at 400 or 600 mg per day per the treating investigator's discretion. Pazopanib can be dose escalated in 200 mg increments to a maximum dose of 800 mg per day at day 1 visits, or earlier intervals, per usual clinical practice. Pazopanib can be dose de-escalated in 200 mg increments to a minimum dose of 200 mg per day. If dose reduction below 200 mg daily is needed, the drug should be permanently

discontinued. Patients may undergo dose re-escalation after prior dose de-escalation at the investigator's discretion per usual clinical practice.

Management guidelines for dose modification of pazopanib are consistent with guidelines from the FDA label, where available. Investigators may also consult the FDA label/package insert prescribing information for pazopanib.

AERS reporting may be required for some adverse events (See Section 9.0).

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

Dose Levels

Dose Level	Pazopanib
Dose Level 1	200 mg daily
Dose Level 2	**400 mg daily**
Dose Level 3	**600 mg daily**
Dose Level 4	800 mg daily
Dose level 2 or 3 may be used as the starting dose per the treating investigator's discretion. See Section 7.2.	

Management of Hematologic Toxicity

Observed Toxicity	Recommended Management
ANC < 1000/μL Platelets < 50,000/μL Grade 3 or 4 neutropenic fever Grade 3 thrombocytopenia with bleeding Other hematologic adverse events ≥ grade 3 deemed clinically significant by the treating investigator.	Interrupt pazopanib. Monitor complete blood count at least weekly. When ANC and platelets improved to grade ≤ 2 (and any infection or bleeding event is resolved), resume at one dose level lower for pazopanib.

Management of Non-Hematologic Toxicity

Hepatic Toxicity

Observed Toxicity	Recommended Management
AST or ALT < 5 * ULN or Bilirubin ≤ 3	Continue pazopanib at the investigator's discretion with weekly monitoring until improved to ≤ grade 1 or baseline.

AST or ALT ≥ 5 * ULN or Bilirubin > 3 * ULN	Interrupt pazopanib with weekly monitoring until improved to ≤ grade 1 or baseline. Resume pazopanib at one dose level lower (and no higher than 400 mg, whichever is lower), and monitor hepatic function weekly for at least 8 weeks. If recurrent AST/ALT ≥ 5 * ULN, permanently discontinue pazopanib.
AST or ALT > 3 * ULN and bilirubin > 1.5 * ULN	Permanently discontinue pazopanib and monitor hepatic function weekly until resolution. In patients with known Gilbert's syndrome and mild, indirect hyperbilirubinemia, manage per recommendations for isolated ALT elevations.

Cardiovascular Toxicity

Absolute decrease in left ventricular ejection fraction of 10% or more from baseline and less than lower limit of normal, or clinical evidence of cardiomyopathy or heart failure.	Interrupt pazopanib. Refer to cardiology. If clinical symptoms resolve and left ventricular ejection fraction improves to within the normal range, resume treatment at one dose level lower at the investigator's discretion.
Grade 3 hypertension	Interrupt pazopanib. Consult a cardiologist or nephrologist if indicated. Begin anti-hypertensive regimen or modify the existing regimen. Resume pazopanib at one dose level lower when blood pressure has improved to ≤ grade 2.
Grade 4 hypertension, hypertensive emergency, malignant hypertension	Permanently discontinue pazopanib.
Grade 2 or 3 venous thrombosis requiring anticoagulation	Interrupt pazopanib. If the planned duration of full dose anticoagulation is ≤ 2 weeks, omit pazopanib until anticoagulation is completed, then resume pazopanib at same dose. If the planned duration of full dose anticoagulation is > 2 weeks, resume pazopanib at the same dose during anticoagulation if the patient is on a stable dose of anticoagulation and is without increased risk of bleeding in the opinion of the treating investigator.

Recurrent venous thromboembolic events or grade 4 thromboembolic event.	Permanently discontinue pazopanib.
Arterial thromboembolic event of any grade	Permanently discontinue pazopanib.

Proteinuria

Proteinuria with spot urine protein creatinine (UPC) ratio ≥ 2.0 but < 3.0; or urine protein ≥ 2.0 g/24 hours but < 3.0.	Interrupt pazopanib until proteinuria resolves to UPC < 2.0 or urine protein < 2.0 g/24 hours, then resume pazopanib at same dose level.
Proteinuria with UPC ratio ≥ 3.0 and < 4.0 or urine protein ≥ 3.0 g/24 hours and < 4.0 g/24 hours.	Interrupt pazopanib until proteinuria resolves to UPC < 2.0 or urine protein < 2.0 g/24 hours. Once resolved, resumed pazopanib at one dose level lower.
Proteinuria with UPC ratio ≥ 4, or urine protein ≥ 4.0 g/24 hours, or clinical nephrotic syndrome.	Permanently discontinue pazopanib.

Other Toxicity

Any perforation, fistulization, leak or wound dehiscence attributed to pazopanib.	Permanently discontinue pazopanib.
Grade 3 or 4 hypothyroidism or hyperthyroidism	Permanently discontinue pazopanib.
Grade 3 or 4 toxicity not otherwise specified.	Interrupt. When improved to baseline, grade 1 or tolerable grade 2, resume treatment at one dose level lower, except for grade 3 fatigue, nausea or vomiting lasting < 5 days with optimization of supportive care, in which case treatment may resume at the same dose level.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at

ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found in Appendix VI. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

9.1 Routine Adverse Event Reporting

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 according to the study calendar in Section 5.0.

9.1.1 Rave CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of 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. **Sites must initiate all AEs for this study in Medidata Rave**.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules 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 (i.e., checking the box *Send All AEs for Evaluation* and save the 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. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP- AERS.

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 members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*; and
- Additional resources: *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/aeguide lines.pdf.

9.1.2 Solicited adverse events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)	PRO-CTCAE Term
Fatigue	General disorders and administrative site conditions	Fatigue
Nausea	Gastrointestinal disorders	Nausea
Diarrhea	Gastrointestinal disorders*	Diarrhea
Anemia	Blood and lymphatic system disorders	
White blood cell decreased	Investigations	
Neutrophil count decreased	Investigations	
Platelet count decreased	Investigations	
Alanine aminotransferase increased	Investigations	
Aspartate aminotransferase increased	Investigations	

* At baseline, the number of stools per day will be collected.

Symptomatic adverse events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine Adverse Event data.

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the

Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs).

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) **Adverse Events CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date.

b) **Adverse Events: Late CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date, or as part of the Clinical Follow-up Phase or Survival Follow-up Phase.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

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

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

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

[1]SAEs 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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

9.3.2 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Alliance A092104 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Exclusions

Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.

Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.

Death

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions."

Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy loss and death neonatal

Pregnancy loss is defined in CTCAE as "Death in utero." Any 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.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

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.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE 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 Rave.

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 unless otherwise specified.

9.4 CAEPRs

9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Olaparib (AZD2281, NSC 747856)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). 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 4499 patients. Below is the CAEPR for Olaparib (AZD2281).

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7 July 9, 2025[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 4499]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia (AIHA))[2]	
		Blood and lymphatic system disorders - Other (pure red cell aplasia (PRCA))[2]	
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 4499]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (drug-induced liver injury (DILI))	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Creatinine increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 4499]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	
VASCULAR DISORDERS			
	Vascular disorders - Other (venous thromboembolism)[3]		

NOTE: New Primary Malignancies other than MDS/AML

New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[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]Autoimmune hemolytic anemia (AIHA) and Pure red cell aplasia (PRCA) have been reported in clinical trials as potential and identified risks when Olaparib is used in combination with durvalumab.

[3]Venous thromboembolism includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis.

[4]Rash includes exfoliative rash, generalized erythema, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.

Adverse events reported on olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Mucositis oral; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Fever; Malaise; Non-cardiac chest pain

IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)

INFECTIONS AND INFESTATIONS - Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Serum amylase increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain

NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus; Rash[4]

VASCULAR DISORDERS - Arterial thromboembolism; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

Note: Olaparib (AZD2281) 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.

9.4.2 Adverse Event List for Pazopanib

Adverse Event	All Grades	Grade 3/4
Fatigue	65%	14%
Diarrhea	59%	5%
Nausea	56%	3%
Weight decreased	48%	4%
Hypertension	42%	7%
Appetite decreased	40%	6%
Hair color changes	39%	0%
Vomiting	33%	3%
Tumor pain	29%	8%
Dysgeusia	28%	0%
Headache	23%	1%
Musculoskeletal pain	23%	2%
Myalgia	23%	2%
Gastrointestinal pain	23%	3%
Dyspnea	20%	5%
Exfoliative rash	18%	< 1%
Cough	17%	< 1%
Peripheral edema	14%	2%
Mucositis	12%	2%
Alopecia	12%	0%
Dizziness	11%	1%
Skin disorder*	11%	2%
Skin hypopigmentation	11%	0%
Stomatitis	11%	< 1%
Chest Pain	10%	2%

Other adverse reactions observed more commonly in patients treated with pazopanib that occurred in ≥ 5% of patients and at an incidence of more than 2% difference from placebo included insomnia (9% versus 6%), hypothyroidism (8% versus 0%), dysphonia (8% versus 2%), epistaxis (8% versus 2%), left ventricular dysfunction (8% versus 4%), dyspepsia (7% versus 2%), dry skin (6% versus < 1%), chills (5% versus 1%), vision blurred (5% versus 2%), and nail disorder (5% versus 0%). * 27 of the 28 cases of skin disorder were palmar-plantar erythrodysesthesia
Data are from the phase 3 study of pazopanib vs placebo in soft tissue sarcoma (n=363) administered as 800 mg once daily or placebo. While these data reflect a large study of pazopanib monotherapy, they may not be fully generalizable to a sarcoma population and when the drug is used in combination with another agent.

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 9.2):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Alkaline phosphatase increased	ALK increased	3	No
Alanine aminotransferase increased	ALT increased	3	No
Aspartate aminotransferase increased	AST increased	3	No
Anorexia	Decreased appetite	3	No
Cough	Cough	2	No
Constipation	Constipation	3	No
Diarrhea	Diarrhea	3	No
Fatigue	Fatigue	3	No
Headache	Headache	3	No

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Nausea	Nausea	3	No
Neutrophil count decreased	Neutropenia	3	No
Platelet count decreased	Thrombocytopenia	3	No
Hyponatremia	Sodium decreased	3	No
Vomiting	Vomiting	3	No

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient. All such events must be reported via CTEP-AERS.

9.4.3 Adverse Event List for Temozolomide

Adverse Event	All Grades	Grade 3/4
Nausea	53%	10%
Vomiting	42%	6%
Headache	41%	6%
Fatigue	34%	4%
Constipation	33%	1%
Convulsions	23%	5%
Hemiparesis	18%	6%
Diarrhea	16%	2%
Asthenia	13%	6%
Fever	13%	2%
Dizziness	12%	1%
Coordination, abnormal	11%	1%
Peripheral edema	11%	1%
Data are from the phase 3 study of temozolomide in anaplastic astrocytoma (n=158) administered as 150 mg/m2 days 1-5 of a 28 day-cycle. While these data reflect the largest study of TMZ monotherapy, they may not be fully generalizable to a sarcoma population and when the drug is used in combination with another agent.		

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 9.2):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Anemia	Anemia	3	No
Anorexia	Decreased appetite	3	No
Cough	Cough	2	No
Constipation	Constipation	3	No
Diarrhea	Diarrhea	3	No
Fatigue	Fatigue	3	No
Headache	Headache	3	No
Nausea	Nausea	3	No
Neutrophil count decreased	Neutropenia	3	No
Platelet count decreased	Thrombocytopenia	3	No
Vomiting	Vomiting	3	No

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient. All such events must be reported via CTEP-AERS.

9.4.4 Adverse Event List for Trabectedin

Adverse Event	All Grades	Grade 3	Grade 4
Nausea	73%	5%	
Fatigue	67%	6%	
Neutropenia	49%	21%	16%
ALT increased	45%	25%	1%
Vomiting	44%	5%	
Anemia	39%	14%	
Constipation	36%	1%	

AST increased	35%	12%	1%
Decreased appetite	34%	2%	
Diarrhea	34%	2%	
Thrombocytopenia	30%	8%	9%
Dyspnea	25%	4%	<1%
Peripheral edema	24%	1%	
Headache	23%	<1%	
ALK increased	20%	1%	
Cough	18%	<1%	
Arthralgia	15%		
Insomnia	15%	<1%	
Myalgia	12%		
Rare (<10%): Decreased left ventricular ejection fraction, hypoesthesia, paresthesia, peripheral neuropathy, pulmonary embolus, rhabdomyolysis.			
Adverse event data from Demetri et. al. (n= 340) and FDA label[24]			

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 9.2):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Anemia	Anemia	3	No
Alkaline phosphatase increased	ALK increased	3	No
Alanine aminotransferase increased	ALT increased	3	No
Aspartate aminotransferase increased	AST increased	3	No
Anorexia	Decreased appetite	3	No
Cough	Cough	2	No
Constipation	Constipation	3	No
Creatinine phosphokinase increased	CPK increased	3	No
Diarrhea	Diarrhea	3	No
Fatigue	Fatigue	3	No
Headache	Headache	3	No

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Nausea	Nausea	3	No
Neutrophil count decreased	Neutropenia	3	No
Platelet count decreased	Thrombocytopenia	3	No
Vomiting	Vomiting	3	No

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient. All such events must be reported via CTEP-AERS.

10.0 DRUG INFORMATION

10.1 General Considerations:

The total administered dose of chemotherapy may be rounded up or down within a range of 10% of the actual calculated dose.

It is not necessary to change the doses of temozolomide or trabectedin due to changes in weight unless the calculated dose changes by >10%.

All study agents are to be administered at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

10.2 CTEP agent ordering, accountability and inventory records, IB availability, and contacts

10.2.1 Ordering NCI-Supplied Agents

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number 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.

Sites may order supplies once a patient has been enrolled to the trial.

Submit agent requests through the PMB Online Agent 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.

10.2.2 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from 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 on this protocol.

10.2.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

10.2.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Registration: 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/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: 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)

10.3 Olaparib (AZD2281), *IND #[redacted], IND Holder: NCI DCTD, NSC#747856*

Description

Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one

Other Names: AZD2281; KU-0059436; CO-CE 42, Lynparza

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

Molecular Formula: C24H23FN4O3 M.W.: 434.46

Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range

Mode of Action: Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5' diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

Description: crystalline solid

Formulation

AstraZeneca supplies and the CTEP, DCTD distributes olaparib as green, film-coated tablets in 100 mg and 150 mg strengths.

- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg are 14.5 mm x 7.25 mm oval-shaped

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

Storage

Store in a secure location below 30° C (86° F).

If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability

Shelf-life studies are ongoing. Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

Route and Method of Administration

Oral. Take tablets without regard to meals.

Potential Drug Interactions

In vivo data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro data shows olaparib is a substrate for P-glycoprotein (P-gp), but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), organic cation transporter 1 (OCT1), multi-drug resistance protein 2 (MRP-2) efflux transporter or breast cancer resistance protein (BCRP). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

Based on in vitro data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. In vitro studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

Patient Care Implications

Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use contraception according to what is specified in the protocol document. It is not known whether olaparib is found in seminal fluid, so as a precaution, male study participants must use a condom according to what is specified in the protocol document. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Lactation is a protocol exclusion criterion and not advised since there is potential for serious adverse reactions in breastfed infants. Advise lactating women to not breastfeed during study treatment and for one (1) month after receiving the last dose of olaparib.
Adverse Events

See CAEPR in Section 9.4.1.

Nursing Guidelines

- Olaparib may be administered with or without food. Patients must be instructed to swallow pills whole.
- Patients should be instructed to avoid grapefruit or grapefruit juice while taking olaparib.
- Assess patient's medication list including OTC and herbal products while patients are taking olaparib as there are many drug to drug interactions.
- Instruct patients to report any edema. Rarely patients may experience venous thrombosis.
- Patients may experience headache, dizziness while on olaparib. Instruct patients to use caution when doing tasks that require attention, until they can ascertain their tolerability to olaparib.
- Gastrointestinal side effects are common, including nausea, vomiting, diarrhea, etc. Treat symptomatically and monitor for effectiveness.
- Monitor CBC w/diff as cytopenias are common. Instruct patients to report any unusual bruising or bleeding and/or signs symptoms of infection to the study team.
- Monitor renal function and assess for any urinary symptoms. Patients may experience urinary tract infection and/or increased creatinine.
- Patients may experience rhinitis, respiratory tract infection, cough, etc. Treat symptomatically and monitor for effectiveness of intervention.

10.4 Pazopanib (GW786034, Votrient, *NSC*#737754)

Description

Chemical Name: 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2 methylbenzene sulfonamide monohydrochloride

Other Names: Pazopanib HCl, GW786034B (the suffix B denotes the monohydrochloride salt), Votrient.

Classification: VEGFR tyrosine kinase inhibitor

Molecular Formula: C21H23N7O2S-HCl **M.W.:** 474.0 (monohydrochloride salt)
437.5 (free base)

Approximate Solubility: The monohydrochloride salt is very slightly soluble in 0.1 M HCl (0.65 mg/mL), and is practically insoluble in pH 7.0 phosphate buffer (0.00005 mg/mL), and in pH 11 piperidine buffer (0.0002 mg/mL).

Mechanism of Action: Pazopanib is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3), platelet derived growth factor receptor (PDGFR alpha and beta) and C-Kit. Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.

Agent ordering and agent accountability

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Pazopanib is available as a 200 mg tablet. Pazopanib is commercially available and not provided by the study.

Storage

Store tablets at room temperature (20° C to 25° C or 68° F to 77° F); excursions permitted to 15° C to 30° C (59 F° to 86° F) [USP controlled room temperature].

Route and Method of Administration

Oral. Take on an empty stomach either 1 hour before or 2 hours after food. The tablets should be swallowed whole and cannot be crushed or broken. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Potential Drug Interactions

In vitro data indicate that pazopanib is primarily metabolized by CYP3A4 isoenzyme with minor contributions from CYP 1A2 and 2C8. Potent CYP3A4 inducers and inhibitors are prohibited on pazopanib trials. Pazopanib is also a substrate for p-glycoprotein and breast cancer resistance protein (BCRP) transporters and concomitant administration of inhibitors such as lapatinib will result in increased plasma pazopanib concentrations.

Clinical studies indicate that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 and not an inhibitor of CYP 2C9, 2C19 or 1A2. Use caution when combining pazopanib with CYP3A4, CYP2C8, and CYP2D6 substrates known to have a narrow therapeutic window.

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1. Pazopanib may increase concentrations of drugs primarily eliminated through these systems.

Avoid co-administration of pazopanib with medicines that increase gastric pH. If the concomitant use of a proton pump inhibitor (PPI) is medically necessary, pazopanib should be taken without food once daily in the evening with the PPI. If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist. Administer pazopanib at least 1 hour before or 2 hours after administration of short-acting antacids.

Avoid co-administration of pazopanib with simvastatin. Concomitant use of pazopanib and simvastatin increases the risk of ALT elevation. Data are not sufficient to assess the risk of concomitant administration of other statins and pazopanib.

Precautions: Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Monitor ECGs and serum electrolytes (e.g., calcium, magnesium, potassium) at baseline and periodically and maintain within the normal range.

For patients who develop hepatic impairment, refer to the protocol document for appropriate dose modification or dose delay.

Advise women study participants of reproductive potential to use effective contraception methods while receiving study treatment and for 2 weeks after the last dose of pazopanib. Men receiving study treatment should be advised to use condoms during sexual intercourse and for at least 2 weeks after the last dose of pazopanib to avoid potential drug exposure to pregnant partners and women partners of reproductive potential. Refer to the protocol document for specific guidance.

Refer to package insert for drug-drug interactions

Adverse Events

See Section 9.4.2.

Pharmacokinetics

Metabolism: Hepatic; primarily via CYP3A4, minor metabolism via CYP1A2 and CYP2C8

Excretion: Feces (primarily); urine (<4%)

Time to peak: Plasma: 2 to 4 hours

Half-life elimination: ~31 hours

Protein binding: >99%

Bioavailability: The AUC and Cmax are increased by ~2-fold with a meal (high-fat or low-fat). If tablets are crushed, the AUC is increased by 46%, the Cmax is increased by 2-fold, and the Tmax is decreased by ~2 hours (do not crush tablets).

Nursing Guidelines

- Pazopanib should be taken without food (1 hour before or 2 hours after a meal). Should be taken whole with water and not broken or crushed. If a dose is missed, do not take if it is less than 12 hours until the next dose.
- There are numerous drug to drug interactions between pazopanib and other agents metabolized through the P450 system. Assess patient's concomitant medications, including OTC and herbal products.
- Hypertension is a commonly reported side effect. Monitor blood pressure closely per study guidelines. Administer anti-hypertensives as ordered by MD.

- Inform patient of possible changes in hair color.
- Gastrointestinal side effects are common (diarrhea, nausea, vomiting, loss of appetite). Treat symptomatically and assess for effectiveness.
- Due to the similarity in nature of this agent to other VEGF inhibitors (bevacizumab, VEGF-trap, etc.) monitor for signs of bleeding, thrombosis and PE. Instruct patient to report any calf tenderness, shortness of breath, chest pain or bleeding immediately.
- Cytopenias are common. Monitor CBC w/diff and instruct patient to report any unusual bruising or bleeding and/or signs of infection to study team.
- Monitor LFT's. Patients who have AST/ALT levels > 3x ULN and concurrent bilirubin >2X ULN should permanently discontinue pazopanib. Patients with AST/ALT levels as above and mild hyperbilirubinemia (with suspected or known Gilbert's syndrome) should be monitored weekly while continuing pazopanib.
- Cardiac side effects (CHF, MI, chest pain, etc.) while rare can be serious and life threatening. Instruct patient to report any cardiac symptoms to study team immediately.
- RPLS, CVA, and TIA are uncommon, but are life threatening. Instruct patient to report any neurological symptoms to the study team immediately.

10.5 Temozolomide (Temodar, NSC362856)

Agent ordering and agent accountability

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Temozolomide is available as 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules

Storage

Store capsules at room temperature.

Administration

Swallow capsules whole with a full glass of water; do not open or chew. Administer consistently with respect to food (either consistently fasting or non-fasting). Administer on an empty stomach in the am. Do not repeat dose if vomiting occurs after dose is administered; wait until the next scheduled dose. If capsules are accidently opened or damaged, avoid inhalation or contact with skin or mucous membranes.

Drug Interactions

Refer to package insert for drug-drug interactions.

Pharmacokinetics (from Facts and Comparisons)

Absorption

Oral: Rapid and complete (100% bioavailable)

Distribution

Vd: Parent drug: 0.4 L/kg. Temozolomide penetrates blood-brain barrier; cerebrospinal fluid levels are ~35% to 39% of plasma levels

Metabolism

Prodrug, hydrolyzed to the active form, MTIC; MTIC is eventually eliminated as CO2 and 5-aminoimidazole-4-carboxamide (AIC), a natural constituent in urine; CYP isoenzymes play only a minor role in metabolism (of temozolomide and MTIC)

Excretion

Urine (~38%; parent drug 6%; AIC 12%); feces <1%.

Clearance: 5.5 L/hour/m2; pediatric subjects 3 to 17 years have similar temozolomide clearance as adults.

Time to peak

Oral: Median: 1 hour; with food (high-fat meal): 2.25 hours.

Half-life elimination

Mean: Parent drug: Children: 1.7 hours; Adults: 1.8 hours

Protein binding

15%

Adverse Events

Consult the package insert for the most current and complete information.

See Section 9.4.3.

Nursing Guidelines

- Myelosuppression has been found to be the dose-limiting toxicity. Gr 3 thrombocytopenia occurred in 6% of patients and Gr 4 in 1%. Gr 3 and Gr 4 lymphopenia occurred in 55% of patients. Leukopenia, lymphopenia, thrombocytopenia and anemia usually occur 2-8 weeks after initiation of treatment. Monitor CBC carefully and report any significant changes to MD. Instruct patient to report signs/symptoms of infection, unusual bruising and bleeding to health care team.
- In previous studies, patients have developed pneumocystis carinii pneumonia (PCP) when taking concomitant temozolomide and steroids. Instruct patient to report any fever, cough, chest pain, of other signs of infection to the health care team. Counsel patients on the importance of taking PCP prophylaxis as prescribed if ordered.
- Advise patient that a mild-moderate rash may be experienced.
- Fatigue may be experienced. Work with patient in energy conserving lifestyle.
- Remind patient that drug needs to be taken on an empty stomach with a full glass of water. Drug should not be crushed, chewed, opened, or dissolved.
- Nausea and vomiting are common. Teach patient to self-medicate with anti-emetics one hour prior to dose. Assess for effectiveness. If vomiting occurs, do not repeat dose. Wait until next scheduled dose.
- Temozolomide may interact with valproic acid by reducing the clearance of temozolomide by 5%. Assess concomitant medication use.
- Constipation is common. Encourage patient to increase fluid intake. Administer stool softeners or laxatives as ordered and monitor for their effectiveness.
- Monitor for cytopenias (i.e. CBC w/differential). Instruct patient to report any fever, signs or symptoms of infection, or any unusual bruising or bleeding to the study team.

- Headache may be seen. Assess for more serious condition (i.e. cerebral bleed, disease progression) first and then treat symptomatically and monitor for effectiveness.

10.6 Trabectedin (Yondelis, NSC#737754)

Agent ordering and agent accountability

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Trabectedin available in 1 mg vial

Storage

Store intact vials at 2-8° C (36-46° F)

Stability

Solutions diluted for infusion should be used within 30 hrs of reconstitution. Infusion should be completed within that 30 hours.

Preparation

Reconstitute the 1 mg vial with 20 mL sterile water for injection resulting in a reconstituted concentration of 0.05 mg/mL. Shake until completely dissolved. Immediately after reconstitution, further dilute for infusion in 500 mL sodium chloride 0.9% or dextrose 5% in water. Diluted solution is compatible in type I glass, polyvinyl chloride (PVC) and polyethylene (PE) bags and tubing, PE and polypropylene (PP) mixture bags, polyethersulfone (PES) inline filters, titanium, platinum, or plastic ports, silicone and polyurethane catheters, and pumps with PVC, PE, or PE/PP contact surfaces. Do not mix with other medications.

Administration

Administer trabectedin over 24 hours via a central line.

Infuse through a central line with a 0.2 micron polyethersulfone filter. Infusion must be completed within 30 hours of reconstitution.

Drug Interactions

Trabectedin is a major substrate of CPY3A4. Refer to package insert for drug-drug interactions.

Pharmacokinetics (from Facts and Comparisons)

Distribution: Vdss: >5,000 L

Metabolism: Extensively hepatic; via CYP3A4

Excretion: Feces (58%; only negligible amounts as unchanged drug); urine (6%; only negligible amounts as unchanged drug)

Half-life elimination: ~175 hours

Protein binding: ~97%; to plasma protein

Adverse Events

Consult the package insert for the most current and complete information.

See Section 9.4.3.

Nursing Guidelines

- GI side effects are commonly seen, including nausea, vomiting, diarrhea, constipation and decreased appetite. Treat symptomatically and monitor for effectiveness.
- Monitor CBC with differential as cytopenias can be seen and can be severe.
- Elevated liver function tests are common. Monitor liver function per protocol and inform treating provider of any changes.
- Patients may experience arthralgia and myalgias. Instruct patient to report these to the study team.
- Monitor renal function and encourage patient to stay adequately hydrated.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1[34]). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule for Assessment of Disease

- Baseline imaging should include a CT or MRI of the chest/abdomen/pelvis for all patients to adequately evaluate for distant metastatic disease. CT scans should be done with IV and oral contrast (if clinically indicated) unless allergy prevents administration. If MRI is chosen as imaging modality for following target/non-target lesions then MRI should be used for evaluation of response during the study.
- Repeat imaging to evaluate disease status will be performed every 2 cycles (6 weeks). A window of ±7 days is permitted. Imaging should be performed before a new cycle starts whenever possible.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

- A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.
- A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions:
    - If there is a soft tissue component that has grown since completion of radiation.
    - Bone metastases with a soft tissue component are considered measurable.

11.2.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
    - As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin

lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.3.3 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of [6 weeks, not less than 6-8] weeks (see Section 11.4.3).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.
- Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 11.4.3.

11.4.3 Response Criteria Target Lesions

- All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.
- **Note:** Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.
- **Evaluation of Target Lesions:** Complete Response (CR): All of the following must be true:
  - Disappearance of all target lesions.
  - Each target lymph node must have reduction in short axis to <1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
- **Progression (PD):** At least one of the following must be true:

- At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
- At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
- See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.
    - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
    - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
    - See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.4.4 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
    - Disappearance of all non-target lesions.
    - Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.

- **Progression (PD):** At least one of the following must be true:
    - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
    - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
    - See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.4.5 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.4.3

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the NCCTG protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
Any	Yes	PD

*See Section 11.4.4

12.0 END OF TREATMENT

12.1 Duration of Protocol Treatment

Protocol treatment is to continue until one of the criteria in Section 12.2 applies. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and following up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression, per RECIST criteria.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Patient decides to withdraw from the study.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Clinical progression.
- Patient non-compliance.
- Pregnancy

  All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

  The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor.
- The drug manufacturer can no longer provide the study agent (if applicable).

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients discontinuing study treatment for reasons other than progressive disease will continue following the Study Calendar for disease assessments (imaging) until progressive disease is documented.

Upon progression, patients will be followed every 3 months (±7 days) for the first 2 years, then every 6 months (±14 days) thereafter until 5 years post-randomization or death, whichever comes first. Information must be collected on (a) the first subsequent anticancer treatment received and (b) survival status. Information may be collected by telephone call or clinical visits conducted as standard of care, per investigator's discretion.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

Follow-up for patients who stop due to toxicity

Patients should complete the end-of-treatment visit/short-term follow-up as described in the Study Calendar. All AEs considered at least possibly-related to study treatment will be followed until resolution, stabilization, return to baseline, or until deemed irreversible. The frequency of follow-up and any associated investigations will be determined by the treating investigator as clinically appropriate.

Patients should continue to undergo imaging to evaluate disease status (imaging) as per the Study Calendar until progression of disease occurs or a new non-protocol therapy is initiated. Thereafter, patients should be followed per Section 12.3.1 above.

Follow-up for patients who receive non-protocol therapy

Patients should be followed per Section 12.3.1 above.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This Phase II/III trial is designed to test the efficacy of olaparib plus temozolomide (Arm 1) vs. investigator's choice (identified prior to randomization) (Arm 2) of either trabectedin or pazopanib in patients with advanced uterine leiomyosarcoma after progression on 2 or more lines of prior chemotherapy. The primary objective for the phase 2 portion will be measured by comparing progression-free survival (PFS) between Arms 1 and 2. The primary objective for the phase 3 portion will be measured by comparing overall survival (OS) between Arms 1 and 2.

The assumptions for the median PFS and OS for trabectedin and pazopanib are based on published subset analyses from the phase 3 registration-directed clinical trials conducted with these agents.

A randomized, controlled, multi-center, phase 3 study assigned 518 patients with leiomyosarcoma and liposarcoma to treatment with trabectedin or dacarbazine and was the basis for FDA approval for trabectedin in sarcoma [16]. Hensley, et. al. conducted a subset analysis of that study to evaluate outcomes among the 232 patients with uLMS with at least 2 prior lines of therapy and reported a median PFS of 4.0 months for trabectedin versus 1.5 months for dacarbazine. The median OS was 13.4 months for trabectedin and 12.9 months for dacarbazine [4].

A randomized, controlled, multi-center phase 3 study assigned 372 patients with soft tissue sarcoma to pazopanib or placebo and led to the approval of pazopanib in soft tissue sarcoma [17]. Benson, et. al. conducted a subset analysis evaluating the outcome of patients with uterine sarcoma assigned to pazopanib on this phase 3 study and also on the preceding phase 2 study. In that analysis, 89% of patients with uterine sarcoma had uLMS, and this study represents the most informative benchmark for pazopanib's activity in uLMS [5]. The median PFS and OS associated with pazopanib were 3.0 months and 11.0 months, respectively [5]. In a prospective randomized study of gemcitabine plus pazopanib versus pazopanib alone in patients with pre-treated soft tissue sarcomas, patients with LMS demonstrated a PFS of 3.0 months on pazopanib [31]. In another randomized study of pazopanib versus doxorubicin as first-line treatment in sarcoma patients older than 60 (approximately 30% of whom had uLMS), pazopanib provided a PFS of 4.4 months [32]. In a retrospective observational study of outcomes of soft tissue sarcoma patients treated with pazopanib in the Kaiser group, the median PFS for 40 LMS patients on pazopanib was 3.0 months [33]. In a prospective randomized study of gemcitabine plus pazopanib versus pazopanib alone in patients with pre-treated soft tissue sarcomas, patients with LMS demonstrated a PFS of 3.0 months on pazopanib [31]. In another randomized study of pazopanib versus doxorubicin as first-line treatment in sarcoma patients older than 60 (approximately 30% of whom had uLMS), pazopanib provided a PFS of 4.4 months [32]. In a retrospective observational study of outcomes of soft tissue sarcoma patients treated with pazopanib in the Kaiser group, the median PFS for 40 LMS patients on pazopanib was 3.0 months [33].

Based on the above, we hypothesize that the median PFS and OS in the control arm for patients who have received 2 or more prior lines of treatment would be 4 and 13 months respectively.

Median PFS from the phase II study of olaparib and temozolomide in uLMS conducted by our group and described above was 6.9 months. Five patients in this phase II study had received 2 prior lines of treatment and demonstrated a median PFS of approximately 11.0 months, and 1-year OS rate of 100% (median OS not reached). Given this promising data but acknowledging

the limitations of a small single-arm trial, we hypothesize that the median PFS and OS in the experimental arm will be 8 months and 23 months respectively.

Overall Plan for Analysis

All randomized patients will be considered evaluable for primary endpoints of OS and PFS based on the intent-to-treat principle and regardless of whether or not they initiate treatment. We will tabulate the number (percent) of patients who withdraw consent prior to treatment to monitor the feasibility of the trial design. If the withdraw of consent rate prior to treatment in Arm 2 is $\geq 5\%$ than the withdraw of consent rate prior to treatment in Arm 1, feasibility will be further evaluated by the study team, CTEP, and Alliance DSMB. Summary statistics for patient and tumor characteristics, eligibility rates, length of follow-up, and treatment acceptance rates will be calculated by assigned treatment arms.

Summary statistics for patient and tumor characteristics, eligibility rates, length of follow-up, and treatment acceptance rates will be calculated by assigned treatment arms.

OS and PFS will be estimated using the Kaplan-Meier method [20], where the stratified log-rank test will be used to compare the distributions across the treatment arms. PFS and OS rates at 1 year, 2 years, and 5 years will also be reported, along with 95% confidence intervals. Univariable and multivariable Cox models stratified by the stratification factors used in the randomization will be assessed as well.

13.2 Statistical Design and Analysis for the Phase 2 Portion

13.2.1 Definition

PFS is defined as the time between the date of randomization and the earliest of disease progression (PD) or death. Patients alive without PD, lost to follow-up, or who withdraw consent prior to PD will be censored at the date of their most recent disease assessment for PFS. Patients who start a non-protocol therapy without PD will also be censored at the time of their last disease assessment for PFS. Intention to treat principles will be used. RECIST v1.1 [15] will be used to assess disease status and clinical or symptomatic deterioration will be allowed for the determination of PD.

13.2.2 Statistical Design and Analysis Plan

Assuming a median PFS of 4 months for control arm (Ho), the investigational treatment (olaparib plus temozolomide) will be considered promising if median PFS is increased to 8.0 months (Ha), corresponding to an observed hazard ratio (HR) of 0.5 favoring olaparib plus temozolomide. In addition, the following conditions were assumed for the study design and used in EAST v6.5 software to develop the design: Target power of 90% and 1-sided alpha 0.10.

1. Testing for superiority (1-sided alpha).
2. Accrual of 3 patients/month.
3. Interim analysis for futility at 50% of information utilizing Rho Family spending function (rho=1.675) boundaries [18].
4. Intention to treat principles for analyses.

To test these hypotheses, we will enroll a total of 70 evaluable patients using a 1:1 randomization and with the following stratification factors: ECOG PS (0 or 1 vs. 2) and prior lines of treatment (2 vs. 3 or more). The randomization algorithm will be the dynamic allocation method of Pocock and Simon [20]. Disease assessments will be required every 2 cycles. A minimum of 6 months follow-up for disease status and survival will be required.

Olaparib plus temozolomide will be considered superior if the p-value associated with the stratified LogRank test statistic is ≤ 0.10 at the time we have observed 58 events (i.e. the phase 2 portion of the study has completed and analyzed, with 90% power).

Note that accrual will be halted between the phase 2 and 3 portions of the trial in order to fully assess the phase 2 primary endpoint.

13.2.3 Interim Analysis

There will be one planned interim look for futility at 50% information. If, after the 29th PFS event, the HR comparing Olaparib + temozolomide to trabectedin or pazopanib is greater than 1.0 (p-value > 0.50) then the study will be stopped for futility. Using simulations, the probability of stopping early (i.e. after one of the interim analyses) under the alternative hypothesis is estimated at 8%. These boundaries were created using the Rho Family spending function (rho=1.675) in EAST v6.5 [18].

13.3 Statistical Design and Analysis for the Phase 3 Portion

13.3.1 Definition

OS is defined as the time between the date of randomization and the date of death from any cause. Patients alive at the time of last follow-up, lost to follow-up, or who withdraw consent will be censored at the date of their most recent follow-up for OS.

13.3.2 Statistical Design and Analysis Plan

If the results of the phase 2 design are positive, then accrual to the phase 3 portion will begin. The phase 3 portion is seeking to improve OS from a median of 13 months to 23 months. The following conditions were assumed for the study design and EAST v6.5 software was used to develop the design:

1. Target power of 90% and 1-sided alpha 0.025
2. Testing for superiority (1-sided alpha).
3. Accrual of 3 patients/month.
4. Interim analysis for futility at 50% of information utilizing Rho Family spending function (rho=3.23) boundaries [18].
5. Intention to treat principles for analyses.

A total of N=165 patients with 130 OS events are required for the phase 3 portion of the trial. All evaluable patients from the phase 2 portion will be utilized; therefore, approximately, 95 additional patients will be needed. Olaparib plus temozolomide will be considered superior in terms of OS if the p-value associated with the stratified LogRank test statistic is ≤ 0.025 at the time we have observed 130 events (i.e. the phase 3 portion of the study has passed efficacy, with 90% power).

13.3.3 Interim Analysis

There will be one planned interim look for futility at 50% information. If, after the 65th OS event, the HR comparing Olaparib + temozolomide to trabectedin or pazopanib is greater than 1.0 (p-value > 0.50) then the study will be stopped for futility. These boundaries were created using the Rho Family spending function (rho=3.23) in EAST v6.5.

13.4 Sample Size, Accrual Time, and Study Duration

13.4.1 Sample Size

Up to 165 evaluable patients will be accrued in the event that both phases of the trial fully accrue (i.e. the study successfully passes (1) the phase 2 interim analysis, (2) the final phase 2 analysis, and (3) the phase 3 interim analysis). In addition to these 165 patients, we will plan to enroll another 25 patients to the trial to account for dropouts, considering that the trial does not allow for crossover. Thus, the maximum overall accrual will be 190 patients. Note that phase 2 patients' data will be used in the phase 3 portion of the trial.

13.4.2 Accrual Rate and Study Duration

It is expected that accrual will occur at approximately 3 patients per month. Assuming this trial meets full accrual, it will require approximately 87 months (27 months to accrue to the phase 2 portion plus 6 months to acquire follow up data for phase 2 when the trial will be temporarily suspended for accrual plus 37 months to accrue additional phase 3 patients plus 17 months for data follow up. On the other hand, the phase 2 interim analysis is expected to occur after ~50 patients have been enrolled (i.e. the 29th progression is expected after 50 patients have been enrolled). This corresponds to approximately 17 months after study activation. Accounting for these 2 extremes (i.e. failure at the phase 2 interim analysis (17 months) and full accrual (87 months)) the total study time should be between 17 months (failure at phase 2 interim analysis) and 87 months (full accrual).

If accrual is slower than expected, the study team and Alliance Experimental Therapeutics and Rare Tumors (ETRT) leadership will meet to review reasons to identify barriers to accrual and discuss with CTEP. In this situation, we will consider modifying eligibility criteria to allow enrollment of patients with RECIST evaluable disease only, if this change is felt to increase the accrual rate of the study based on discussion with the site investigators for the study and with CTEP.

13.5 Secondary Endpoint Analysis Plans

13.5.1 Overall Response Rate (ORR)

The ORR will be estimated by dividing the number of evaluable patients that achieve a confirmed response (PR or better) by the total number of evaluable patients. This estimate will be calculated by arm and will also include a 95% confidence interval using the properties of the binomial distribution, and compared between the arms using a chi-square test.

13.5.2 Duration of Response (DOR)

This analysis is restricted to those patients that achieved a confirmed response (PR or better). For these patients, the duration of response is defined as the time from first evidence of response until disease progression (or death). Patients that go off of study treatment prior to progression will have their DOR time censored at that time.

13.5.3 Disease Control Rate (DCR)

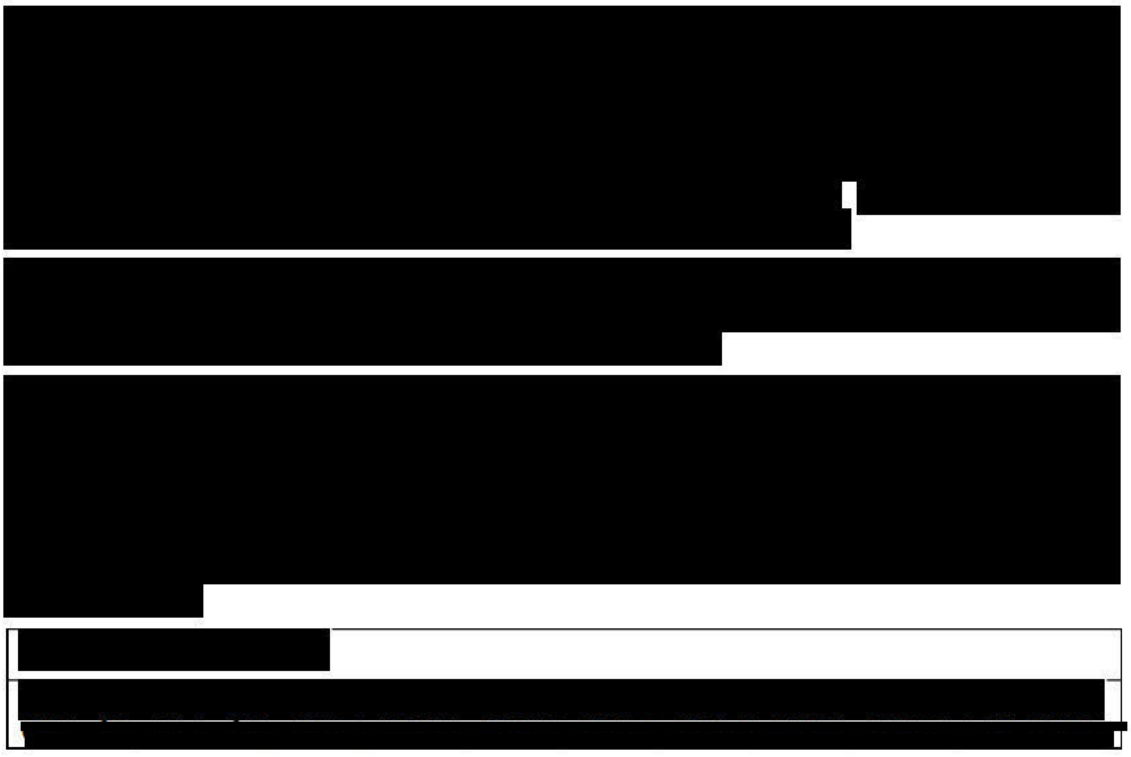
DCR will be estimated by dividing the number of patients that achieve complete response, partial response, or stable disease at the 6 week assessment divided by all evaluable patients. This estimate will be calculated by arm and will also include a 95% confidence interval using the properties of the binomial distribution, and compared between the arms using a chi-square test.

13.5.4 Safety and Tolerability

Adverse events will be recorded using NCI CTCAE v5.0 for each patient. Frequency tables and summary statistics will be used and with the appropriate methods of evaluating categorical and continuous data.

In addition, patient reported safety and tolerability will be assessed using PRO-CTCAE for a prespecified group of expected toxicities. PRO-CTCAE assessments will occur prior to registration and on day 1 of every cycle during treatment. Collection of PRO-CTCAE will be discontinued after cycle 11. To evaluate between-arm differences for each patient-reported symptomatic adverse event (i.e. each item in the questionnaire will be evaluated individually) as assessed by the PRO-CTCAE, the frequency and proportion of patients with a maximum post-baseline score greater than 0 will be compared across arms using a $\chi 2$ test or Fisher's exact test with a nominal significance level of $\alpha = 0.10$. Similarly, the frequency and proportion of patients with a maximum post-baseline score greater than or equal to 3 will be compared across arms using a $\chi 2$ test or Fisher's exact test with a nominal significance level of $\alpha = 0.10$. The same procedure will be applied to patients' maximum baseline-adjusted scores. Patients' maximum baseline-adjusted scores will be calculated using the method described by Dueck et al. [21] If the patient's maximum post-baseline score is greater than his/her baseline score, then the patient's maximum baseline-adjusted score will equal his/her maximum post-baseline score; otherwise, if the patient's maximum post-baseline score is less than or equal to his/her baseline score, then the patient's maximum baseline-adjusted score will equal 0. The aforementioned analyses will be based on all available PRO-CTCAE data. However, the proportion of, and reported reasons for, missing data will be presented by time point and arm. Since a preferred or optimal statistical methodology for PRO-CTCAE data is yet to be determined, additional analyses of PRO-CTCAE data beyond those specified above may be undertaken based on the current state of the science at time of data maturity for this study.

13.6 Exploratory Objective Analysis Plan



[redacted]

13.7 Adverse Event Stopping Rule

This study will be monitored by the Alliance DSMB on a bi-annual basis. In addition, the study chair and study statistician will review the accrual and safety data periodically and in conjunction with the Alliance Group Meeting reports to identify any feasibility problems associated with accrual rates and adverse events.

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also suspend accrual because of unexpected safety signals/adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe adverse events that satisfy any of the following criteria, where AEs regardless of attribution will be considered:

- If at any time up to 15 patients per arm (30 total) that are evaluable for AEs, the number of patients who experience a grade 4 or grade 5 non-hematologic adverse event in one arm exceeds the other by at least 5 patients.
- After 15 total patients are evaluable for AEs in each arm, the number of patients who experience a grade 4 or grade 5 non-hematologic adverse event in one arm exceeds another by at least 5 patients AND at least a 10% difference in AE rates.
- If 4 or more patients in the first 20 patients, and at least 20% after the first 20 patients across both arms experience a grade 3 or 4 febrile neutropenia event that is deemed at least possibly related to study treatment.

13.8 Study Reporting

13.8.1 Alliance DSMB

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, consent withdrawal rates (as noted in Section 13.1), and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.8.2 Data Mapping Utility (DMU)

Data for this study will be submitted via the Data Mapping Utility (DMU) to the NCI. Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: ctep.cancer.gov/protocolDevelopment/dmu.htm.

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU by the Alliance Statistics and Data Management Center in addition to expedited reporting of serious adverse events via CTEP-AERS by the site.

13.8.3 Result Reporting on ClinicalTrials.Gov

At study activation, this study will have been registered within the "https://clinicaltrials.gov/" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. Estimates of treatment effect and the corresponding 95% confidence intervals (CIs) will be provided as follows (with an understanding that sometimes the CI or estimate will not be computable because of scant data).

- Estimates of PFS and OS and the corresponding 95% confidence intervals (CIs) by race.
- Estimates of PFS and OS and the corresponding 95% confidence intervals (CIs) by ethnicity.

13.9 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, sex, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, sex, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and sex groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 20% of patients will be classified as minorities by race and 100% patients will be women. Expected sizes of racial by sex subsets for patients registered randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	9	0	1	0	10
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	17	0	5	0	22
White	128	0	24	0	152
More Than One Race	4	0	0	0	4
Total	160	0	30	0	190

14.0 BIOBANKING FOR FUTURE CORRELATIVE SCIENCE

The optional tissue and blood collection for future studies must be offered to all patients enrolled on Alliance A092104 (although patients may opt to not participate). This collection does not require separate IRB approval. Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

15.0 MONITORING PLAN

Standard Alliance monitoring procedures will be used for this study.

15.1 IRB terminations

Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Please contact the Alliance Regulatory team at regulatory@alliancenctn.org with any questions.

16.0 REFERENCES

1. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecologic oncology 2008; 109(3): 329-34.
2. Sutton G, Blessing J, Hanjani P, Kramer P, Gynecologic Oncology G. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecologic oncology 2005; 96(3): 749-52.
3. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014; 15(4): 415-23.
4. Hensley ML, Patel SR, von Mehren M, et al. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: Subgroup analysis of a phase 3, randomized clinical trial. Gynecologic oncology 2017; 146(3): 531-7.
5. Benson C, Ray-Coquard I, Sleijfer S, et al. Outcome of uterine sarcoma patients treated with pazopanib: A retrospective analysis based on two European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) clinical trials 62043 and 62072. Gynecologic oncology 2016; 142(1): 89-94.
6. Chudasama P, Mughal SS, Sanders MA, et al. Integrative genomic and transcriptomic analysis of leiomyosarcoma. Nat Commun 2018; 9(1): 144.
7. Seligson ND, Kautto EA, Passen EN, et al. BRCA1/2 Functional Loss Defines a Targetable Subset in Leiomyosarcoma. Oncologist 2019; 24(7): 973-9.
8. Rosenbaum E, Jonsonn P, Seier S, et al. DNA damage response pathway alterations and clinical outcome in leiomyosarcoma. J Clin Oncol 2019; 15(37): 11048-.
9. Jonsson P, Bandlamudi C, Cheng ML, et al. Tumour lineage shapes BRCA-mediated phenotypes. Nature 2019; 571(7766): 576-9.
10. Oza J, Doshi SD, Hao L, Musi E, Schwartz GK, Ingham M. Homologous recombination repair deficiency as a therapeutic target in sarcoma. Semin Oncol 2020; 47(6): 380-9.
11. Ingham M, Allred J, Gano K, et al. NCI protocol 10250: A phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma. J Clin Oncol 2021; 39.
12. Baruchel S, Diezi M, Hargrave D, *et al*. Safety and pharmacokinetics of temozolomide using a dose-escalation, metronomic schedule in recurrent paediatric brain tumours. *Eur J Cancer*. 2006;42(14):2335-42.
13. Dhodapkar M, Rubin J, Reid JM, *et al* Phase I trial of temozolomide (NSC 362856) in patients with advanced cancer. *Clin Cancer Res*. 1997;3(7):1093-100.
14. Hammond LA, Eckardt JR, Baker SD, *et al.* Phase I and pharmacokinetic study of temozolomide on a daily-for-5-days schedule in patients with advanced solid malignancies. *J Clin Oncol*. 1999;17(8):2604-13.
15. Farago AF, Yeap BY, Stanzione M, et al. Combination Olaparib and Temozolomide in Relapsed Small-Cell Lung Cancer. Cancer Discov 2019; 9(10): 1372-87.
16. Hanna C, Kurian KM, Williams K, et. al. Pharmacokinetics, safety and tolerability of olaparib and temozolomide for recurrent glioblastoma: results of the phase 1 OPARATIC trial. Neuro Oncol 2020; 22(12) 1840-1850.

17. Garcia del Muro X, Lopez-Pousa A, Martin J et. al. A phase II trial of temozolomide as a 6-week, continous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanish Group for Research on Sarcomas. Cancer 2005; 104(8):1706-1712.

18. Kasper B, Achee A, Schuster K, et al. Unmet Medical Needs and Future Perspectives for Leiomyosarcoma Patients-A Position Paper from the National LeioMyoSarcoma Foundation (NLMSF) and Sarcoma Patients EuroNet (SPAEN). Cancers (Basel) 2021; 13(4).

19. Farago AF, Yeap BY, Stanzione M, et al. Combination Olaparib and Temozolomide in Relapsed Small-Cell Lung Cancer. Cancer Discov 2019; 9(10): 1372-87.

20. Knijnenburg TA, Wang L, Zimmermann MT, et al. Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas. Cell Rep 2018; 23(1): 239-54 e6.

21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-47.

22. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol 2016; 34(8): 786-93.

23. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379(9829): 1879-86.

24. Lan KK, DeMets DL. Changing frequency of interim analysis in sequential monitoring. Biometrics 1989; 45(3): 1017-20.

25. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31(1): 103-15.

26. Kaplan E, Meier P. Nonparametric estimation for incomplete observations. J Am Stat Assoc 1958; 53.

27. Dueck AC, Scher HI, Bennett AV, Mazza GL, Thanarajasingam G, Schwab G, Weitzman AL, Rogak LJ, Basch E. Assessment of Adverse Events From the Patient Perspective in a Phase 3 Metastatic Castration-Resistant Prostate Cancer Clinical Trial. JAMA Oncol. 2020 Feb 1;6(2):e193332.

28. Sztupinszki Z, Diossy M, Krzystanek M,et. al. Migrating the SNP array-based homologous recombination deficiency measures to next generation sequencing data of breast cancer. NPJ Breast Cancer 2018;4(16)eCollection.

29. Knijnenburg TA, Wang L, Zimmerman MT, et. al. Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas. Cell Rep. 2018 23(1):239-254.

30. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A et. al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized, Multicenter Clinical Trial. J Clin Oncol 2016 34(8) 786-793.

31. Schmoll HJ, Lindner LH, Reichardt P et. al. Effiacy of Pazopanib With or Without Gemcitabine in Patients with Anthracycline- and/or Ifosfamide-Refractory Soft Tissue Sarcoma. JAMA Oncol 2021;7(2):255-262.

32. Grunwald V, Karch A, Schuler M, et. al. Randomized Comparison of Pazopanib and Doxorubicin as First-Line Treatment in Patients with Metastatic Soft Tissue Sarcoma Age 60 Years or Older: Results of a German Intergroup Study. J Clin Oncol 2020;38(30):3555-3564.

33. Seto T, Song MN, Trieu M et al. Real-World Experiences with Pazopanib in Patients with Advanced Soft Tissue and Bone Sarcoma in Northern California. Med. Sci. 2019;7(3).

34. Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-247, 2009.

APPENDIX I: CRADA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") 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 Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) 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.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other 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"):

a. NCI will provide all Collaborators with prior 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 that would tend to restrict NCI's participation in the proposed combination protocol.

b. 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 Agent.

c. 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.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), 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.

4. 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.

5. Any data provided to Collaborator(s) for Phase 3 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.

6. 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 Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) 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 Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) 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:

Email: ncicteppubs@mail.nih.gov

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

APPENDIX II: PATIENT CLINICAL TRIAL WALLET CARD

Version #01

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: A092104

Study Drug(S): Olaparib, temozolomide, trabectedin, pazopanib

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX III: A092104 OLAPARIB MEDICATION DIARY

Today's date _____

Patient Name_____ (initials acceptable) **Patient Study ID** _____

INSTRUCTIONS FOR THE PATIENT:

1. Complete this form while you take **olaparib**. This form is a 21 day diary. You may need to complete more than one form between clinic visits.
2. You will take your dose of **olaparib twice a day for 7 consecutive days followed by 14 days off.** One dose of olaparib should be taken together with temozolomide at approximately the same time (morning or night) of each day.
3 Your dose of olaparib is ____ mg twice daily which should be taken as ____ (# of tablets) ____ (strength of tablets in mg) twice daily.
4 Take the **olaparib tablets** with water and consistently take with or without food. This includes when taking olaparib with **temozolomide**. Temozolomide can be taken with or without food but it may be better tolerated if taken on an empty stomach.
5. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
6. If vomiting occurs after the olaparib tablets are swallowed, the dose should only be replaced **if** all of the intact tablets can be seen and counted. If a scheduled dose of olaparib for any reason is missed, take the scheduled dose of olaparib **up to a maximum of 2 hours** after the scheduled dose time. **If more than 2 hours** after the scheduled dose time, the missed dose of olaparib is not to be taken and take the next dose at the next scheduled time..
7. Swallow tablets whole, do not crush or chew. Do not dissolve tablets in water.
8. You should not have grapefruit, grapefruit juice, or Seville oranges while on this study.
9. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
10. Please return this form to your doctor at your next appointment. You may need to return more than one form per clinic visit. You will also be asked to return your pill bottles at each visit.

Date	Day	Number of olaparib tablets taken in the Morning	Time of Morning Dose	Number of olaparib tablets taken in the Evening	Time of Evening Dose	Comments
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8	No Dose	-	No Dose	-	
	9	No Dose	-	No Dose	-	
	10	No Dose	-	No Dose	-	
	11	No Dose	-	No Dose	-	
	12	No Dose	-	No Dose	-	
	13	No Dose	-	No Dose	-	
	14	No Dose	-	No Dose	-	
	15	No Dose	-	No Dose	-	
	16	No Dose	-	No Dose	-	
	17	No Dose	-	No Dose	-	
	18	No Dose	-	No Dose	-	
	19	No Dose	-	No Dose	-	
	20	No Dose	-	No Dose	-	
	21	No Dose	-	No Dose	-	

Patient's Signature: _____ Date: _____

Staff Signature: _____ Date: _____

(To be completed by Staff)

Number of Pills Given:_____ Pill Bottle(s) returned: Circle Yes or No

Total Daily Dose:_____ mg twice daily Number of Pills returned:_____

APPENDIX IV: A092104 TEMOZOLOMIDE MEDICATION DIARY

Today's date _____

Patient Name_____ (initials acceptable) **Patient Study ID** _____

INSTRUCTIONS FOR THE PATIENT:

1. Complete this form while you take **temozolomide**. This form is a 21 day diary. You may need to complete more than one form between clinic visits.
2. You will take your dose of **temozolomide once a day for 7 consecutive days followed by 14 days off. Temozolomide should be taken together with the morning dose or the evening dose of olaparib, at approximately the same time each day.**
3. Your dose of temozolomide is ____ mg once daily.

   To make up this dose, you will take temozolomide capsules together as follows:

   ____ (# of capsules) ____ (strength of capsules in mg), plus

   ____ (# of capsules) ____ (strength of capsules in mg), plus

   ____ (# of capsules) ____ (strength of capsules in mg)
4. Take the **temozolomide capsules** with water at least one hour before a meal or at least two hours afterwards. Temozolomide can be taken with or without food, but it may be better tolerated if taken on an empty stomach [(i.e. in the fasted state, either 1 hour before, or 2 hours after, a meal]). Take consistently with or without food. This includes when taking **olaparib** with temozolomide.
   For the first cycle of treatment, take ondansetron 8 mg approximately 30 minutes prior to taking the temozolomide to help prevent nausea. From cycle 2 onward, the use of ondansetron prior to temozolomide dosing is optional
5. Record the date, the number of capsules of each strength that you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
6. If a dose is missed for any reason (such as forgetting to take the capsules or vomiting), do not make up that dose; resume dosing with the next scheduled dose.
7. If capsules are accidently opened or damaged, avoid inhalation or contact with skin or mucous membranes.
8. Swallow capsules whole, do not crush or chew. Do not dissolve capsules in water.
9. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
10. Please return this form to your doctor at your next appointment. You may need to return more than one form per clinic visit.

Date	Day	Number of ___ mg temozolomide capsules taken	Number of ___ mg temozolomide capsules taken	Number of ___ mg temozolomide capsules taken	Time Taken	Comments
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8	No Dose	-		-	
	9	No Dose	-		-	
	10	No Dose	-		-	
	11	No Dose	-		-	
	12	No Dose	-		-	
	13	No Dose	-		-	
	14	No Dose	-		-	
	15	No Dose	-		-	
	16	No Dose	-		-	
	17	No Dose	-		-	
	18	No Dose	-		-	
	19	No Dose	-		-	
	20	No Dose	-		-	
	21	No Dose	-		-	

Patient's Signature: _____ Date: _____

Staff Signature: _____ Date: _____

(To be completed by Staff)

Number of Pills Given:_____ Pill Bottle(s) returned: Circle Yes or No

Total Daily Dose:_____ mg once daily Number of Pills returned:_____

APPENDIX V: A092104 PAZOPANIB MEDICATION DIARY

Today's date _____

Patient Name_____ (initials acceptable) **Patient Study ID** _____

INSTRUCTIONS FOR THE PATIENT:

1. Complete this form while you take **pazopanib**. This form is a 21 day diary. You may need to complete more than one form between clinic visits.
2. Your dose of **pazopanib** is ____ mg once daily which should be taken as ____ (# 200 mg tablets) once daily.
3 Take the **pazopanib tablets** with water at least one hour before a meal or at least two hours afterwards. Take consistently with or without food.
4. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
5. If a dose is missed, or if vomiting occurs after dose is administered do not make up that dose if it is less than 12 hours until the next dose; resume dosing with the next scheduled dose.
6. Swallow tablets whole, do not crush or chew. Do not dissolve tablets in water.
7. You should not have grapefruit, grapefruit juice, or Seville oranges while on this study.
8. In rare cases this medication can cause the following side effects:
   a) If you develop unusually severe, persistent or worsening pain in your abdomen.
   b) If you are unable to pass stools and gas, and your abdomen feels uncomfortably bloated.

   If these occur, stop taking the pazopanib tablets and call your doctor/health care provider.
9. If concurrent use of a gastric acid-reducing agent cannot be avoided, consider short-acting antacids in place of proton pump inhibitors and H2-receptor antagonists; separate pazopanib administration from short-acting antacids by several hours. Consult your pharmacist.

   If these occur, stop taking the pazopanib tablets and call your doctor/health care provider.
10. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am.
11. Please return this form to your doctor at your next appointment. You may need to return more than one form per clinic visit. You will also be asked to return your pill bottles at each visit.

Date	Day	Number of pazopanib tablets taken	Time Taken	Number of pazopanib tablets missed	Comments
	1				
	2				
	3				
	4				
	5				
	6				
	7				
	8				
	9				
	10				
	11				
	12				
	13				
	14				
	15				
	16				
	17				
	18				
	19				
	20				
	21				

Patient's Signature: _____ Date: _____

Staff Signature: _____ Date: _____

(To be completed by Staff)

Number of Pills Given:_____ Pill Bottle(s) returned: Circle Yes or No

Total Daily Dose:_____ mg once daily Number of Pills returned:_____

APPENDIX VI: ECOG PERFORMANCE STATUS SCALE

GRADE	ECOG PERFORMANCE STATUS
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

APPENDIX VII: NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.