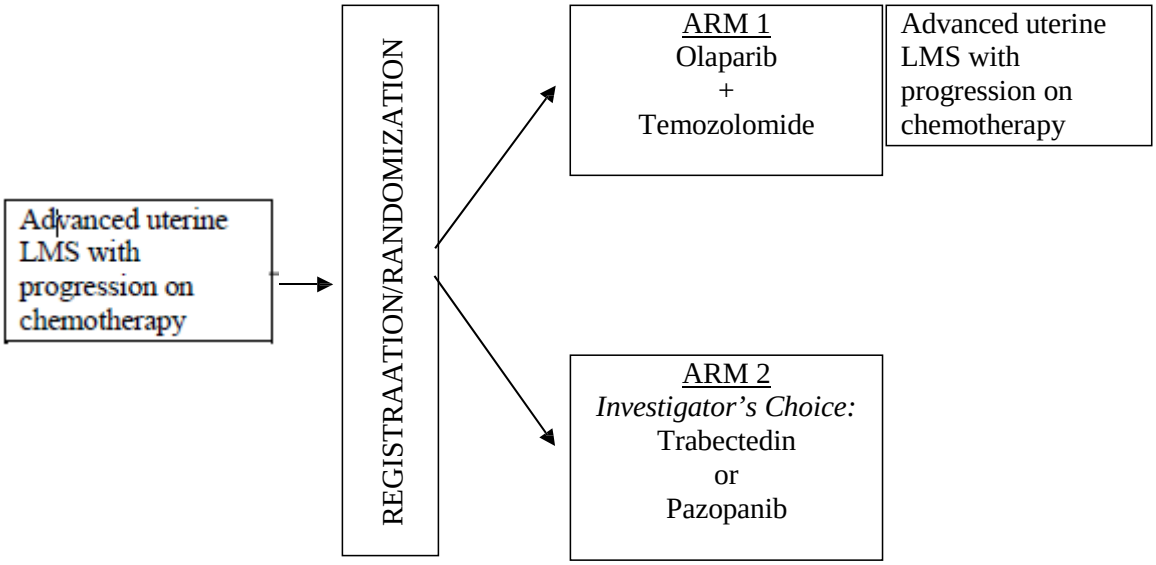
Schema
1 Cycle = 21 Days



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.

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.

3.1 PATIENT SELECTION

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

3.2 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.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

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).

3.3 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).

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 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 VII)

___ **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 at least one of the agents included on the investigator's choice arm: trabectedin or pazopanib. If the patient has had prior treatment with one of these agents, 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 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.

___ **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.
- 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 VIII). 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.

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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 8.1.9 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 8.1.10 for more information.

3.2.12 Language

In order to complete the mandatory patient-completed measure, participants must be able to speak and/or read English and Spanish.

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.