Cancer Research Consortium of West Michigan
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FAST FACTS

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

Eligibility Criteria

1. Documentation of Disease:
    a. 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.
    b. Metastatic or locally advanced and surgically unresectable disease, in the opinion of the treating investigator.
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. 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.
4. Age ≥ 18 years
5. ECOG Performance Status ≤ 2 (See Appendix VII)
6. Prior Treatment
    a. 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.
    b. Patients may not have received prior treatment with any PARP inhibitor, temozolomide or dacarbazine (IV analogue of temozolomide).
    c. 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.
    d. 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.
    e. Patients must have completed all prior anti-cancer treatment, including radiation, ≥ 28 days prior to registration.
7. Prior Surgery
    a. 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.

8. Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	$\geq 1500/mm^3$
Platelet count	$\geq 100{,}000/mm^3$
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.

9. Comorbidities – Cardiovascular Conditions

a. 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.

b. 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.

c. Patients may not have an uncontrolled ventricular arrhythmia or recent (within 3 months) myocardial infarction

d. 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.

10. Comorbid Comorbidities – Other Conditions

a. Patients may not have a history of active or unresolved: perforation, abscess or fistula within 28 days prior to registration (either clinically or radiographically).

b. 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.

c. Hepatitis B: For patients with evidence of chronic hepatitis B (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

d. 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.

e. HIV/Immunosuppressive Conditions: HIV-infected patients on effective antiretroviral therapy with undetectable viral load within 6 months are eligible for this trial.

f. 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.

g. 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.

h. 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.

i. Patients must be able to swallow oral medications.

11. Concomitant medications

a. 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.

b. 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.

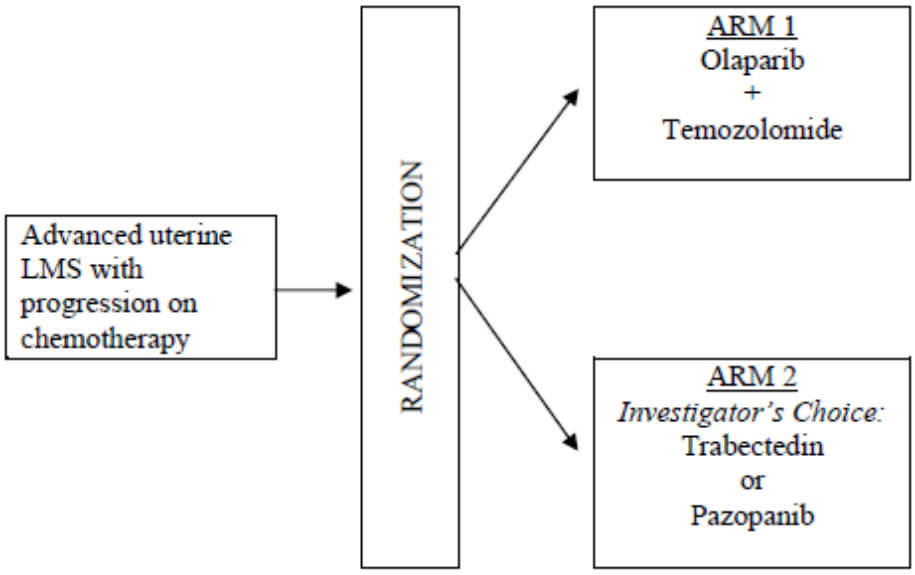
12. Language

a. 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.

13. Investigator's Choice Arm Assignment and Eligibility

a. 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.



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)