Cancer Research Consortium of West Michigan
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Fast Facts

NRG GY005: A Randomized Phase II/III study of the combination of Cediranib and Olaparib compared to Cediranib or Olaparib alone, or Standard of care chemotherapy in women with recurrent platinum-resistant or -refractory ovarian, fallopian tube, or primary peritoneal cancer (COCOS)

ELIGIBILITY CRITERIA

1. Patients must have histologically or cytologically confirmed ovarian cancer, peritoneal cancer or fallopian tube cancer and must have a histological diagnosis of either serous or endometrioid cancer based on local histopathological findings. Both endometrioid and serous histology should be high-grade for eligibility of non-mutation carriers. Patients with clear cell, mixed epithelial, undifferentiated carcinoma, or transitional cell carcinoma histologies are also eligible, provided that the patient has a known deleterious germline BRCA1 or BRCA2 mutation identified through testing at a clinical laboratory.
   Note: Due to the long acceptance of BRCA testing through Myriad, Myriad testing will be accepted. If testing for BRCA is done by other organizations, documentation from a qualified medical professional (e.g., ovarian cancer specialty physician involved in the field, high risk genetics physician, genetics counselor) listing the mutation and confirming that the laboratory results showed a recognized germ line deleterious BRCA 1 or BRCA 2 mutation or BRCA rearrangement is required. A copy of Myriad or other BRCA mutational analysis (positive or VUS or negative) reports will be requested but not required for study enrollment.

2. Patients should have recurrent platinum-resistant or- refractory disease - defined as disease that has progressed by imaging while receiving platinum or had recurrence within 6 months of the last receipt of platinum-based chemotherapy. Rising CA125 only is not considered as platinum-resistant or refractory disease.

3. Phase II study: measurable disease by RECIST 1.1 criteria. If archival tumor sample is not available tumor sample from fresh biopsy is acceptable. Phase III study: evaluable disease – defined as RECIST 1.1 measurable disease OR non-measurable disease (defined as solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 definitions for target lesions OR ascites and/or pleural effusion that has been pathologically demonstrated to be disease-related in the setting of a CA125 > 2x ULN).

4. Prior therapy:
   a. No more than 3 prior treatment regimens (including primary therapy; no more than 1 prior non-platinum based therapy in the platinum-resistant/-refractory setting). Hormonal therapies used as single agents (i.e. tamoxifen, aromatase inhibitors) will not count towards this line limit.
   b. Patients may not have had a prior anti-angiogenic agent in the recurrent setting. Prior use of bevacizumab in the upfront or upfront maintenance setting is allowed.
   c. Patients may not have previously received a PARP-inhibitor.

5. Patient must have provided study specific informed consent prior to study entry.

6. ECOG performance status 0 or 1 or 2 (see Appendix II).

7. Patients must have adequate organ and marrow function as defined below

- Absolute neutrophil count > 1,500/mcL
- Platelets > 100,000/mcL
- Hemoglobin > 10 g/dL
- Total bilirubin < 1.5 times the upper limit of normal (ULN) institutional limits
- AST (SGOT)/ALT (SGPT) < 3 × institutional ULN. If intrahepatic liver metastases are present, AST and ALT must be ≤ 5 times institutional ULN.
- Creatinine < 1.5 X the institutional ULN
- Urine protein: creatinine ratio (UPC) of ≤1 OR less than or equal to 2+ proteinuria on two consecutive dipsticks taken no less than 1 week apart. UPC is the preferred test. Patients with 2+ proteinuria on dipstick must also have a 24-hour urine collection demonstrating protein of ≤ 500mg over 24 hours.

8. Toxicities of prior therapy (excepting alopecia) should be resolved to less than or equal to Grade 1 as per CTCAE v4.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Patients with long-standing stable grade 2 neuropathy may be considered after discussion with the Study Chair.

9. Adequately controlled blood pressure (SBP ≤140; DBP ≤ 90mmHg) on maximum of three antihypertensive medications. Patients must have a BP of ≤ 140/90 mmHg taken in the clinic setting by a medical professional within 2 weeks prior to starting study. It is strongly recommended that patients who are on three antihypertensive medications be followed by a cardiologist or a primary care physician for management of BP while on protocol. Patients must be willing and able to check and record daily blood pressure readings. Blood pressure cuffs will be provided to patients randomized to cediranib alone and the combination of olaparib and cediranib arms. Please refer to section 9.6, and Appendix IV.

10. Adequately controlled thyroid function, with no symptoms of thyroid dysfunction and TSH within normal limits.

11. Able to swallow and retain oral medications and without GI illnesses that would preclude absorption of cediranib or olaparib.

12. Age ≥ 18 years

13. Cediranib has been shown to terminate fetal development in the rat, as expected for a process dependent on VEGF signaling. For this reason, women of child-bearing potential must have a negative pregnancy test prior to study entry. Women of child-bearing potential must agree to use two reliable forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 weeks after cediranib discontinuation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

14. Olaparib adversely affects embryo-fetal survival and development in the rat. For this reason, women of child-bearing potential must have a negative pregnancy test prior to study entry. Women of child-bearing potential must agree to use must agree to use two reliable forms of contraception (hormonal

or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 3 months after the last dose of olaparib. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

INELIGIBILITY CRITERIA

1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) of starting treatment or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Patients may not have had hormonal therapy within 2 weeks prior to entering the study. Patients receiving raloxifene for bone health as per FDA indication may remain on raloxifene absent other drug interactions.

2. Any other investigational agents within the past 4 weeks.

3. Prior treatment affecting the VEGF/VEGFR pathway or the angiopoietin pathway in the recurrent setting, including but not limited to thalidomide, bevacizumab, sunitinib, sorafenib, pazopanib, cediranib, nintedanib, and trebananib. Bevacizumab used in the upfront setting in conjunction with chemotherapy and/or as maintenance to treat newly diagnosed disease will be allowed.

4. Prior use of PARP-inhibitors.

5. CA-125 only disease without RECIST 1.1 measurable or otherwise evaluable disease.

6. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting cediranib.

7. Current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months prior to starting study drugs

8. History of intra-abdominal abscess within the past 3 months.

9. History of gastrointestinal perforation. Patients with a history of abdominal fistula will be considered eligible if the fistula was surgically repaired or has healed, there has been no evidence of fistula for at least 6 months, and patient is deemed to be at low risk of recurrent fistula.

10. Dependency on IV hydration or TPN.

11. Any concomitant or prior invasive malignancies with the following curatively treated exceptions:
    a. Treated limited stage basal cell or squamous cell carcinoma of the skin.
    b. Carcinoma in situ of the breast or cervix.
    c. Primary endometrial cancer meeting the following conditions: Stage not greater than IA, grade 1 or 2, no more than superficial myometrial invasion, without vascular or
    d. lymphatic invasion; no poorly differentiated subtypes, including papillary serous/serous, clear cell, or other FIGO grade 3 lesions. Prior cancer treated with a curative intent with no evidence of

recurrent disease 5 years following diagnosis and judged by the investigator to be at low risk of recurrence.

12. Patients with untreated brain metastases, spinal cord compression, or evidence of symptomatic brain metastases or leptomeningeal disease as noted on CT or MRI scans should not be included on this study, since neurologic dysfunction may confound the evaluation of neurologic and other adverse events. Patients with treated brain metastases and resolution of any associated symptoms must demonstrate stable post-therapeutic imaging for at least 6 months following therapy prior to starting study drug.

13. Patients with any of the following:
    a. History of myocardial infarction within six months
    b. Unstable angina
    c. Resting ECG with clinically significant abnormal findings.
    d. New York Heart Association functional classification of III or IV

14. If cardiac function assessment is clinically indicated or performed: LVEF less than normal per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines. Patients with the following risk factors should have a baseline cardiac function assessment:
    a. Prior treatment with anthracyclines
    b. Prior treatment with trastuzumab
    c. Prior central thoracic radiation therapy (RT), including RT to the heart
    d. History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)
    e. Prior history of impaired cardiac function

15. History of stroke or transient ischemic attack within six months

16. Clinical significant peripheral vascular disease or vascular disease (aortic aneurysm or aortic dissection)

17. Evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events is permitted.

18. Evidence suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated. No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUBCT).

19. Patients may not use any complementary or alternative medicines including natural herbal products or folk remedies as they may interfere with the effectiveness of the study treatments.

20. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (other than atrial fibrillation with controlled ventricular rate), or psychiatric illness/social situations that would limit compliance with study requirements.

21. Known HIV-positive individuals are ineligible because of the potential for pharmacokinetic interactions with cediranib or olaparib. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy.

22. Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A4 are ineligible. Refer to a frequently updated drug information reference for a list of strong inducers and inhibitors. See Appendix V. Strong inhibitors and inducers of UGT/PgP should be used with caution.

23. Pregnant women are excluded from this study because cediranib and olaparib are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with cediranib and olaparib, breastfeeding should be discontinued if the mother is treated with cediranib or olaparib. These potential risks may also apply to other agents used in this study.

SCHEMA