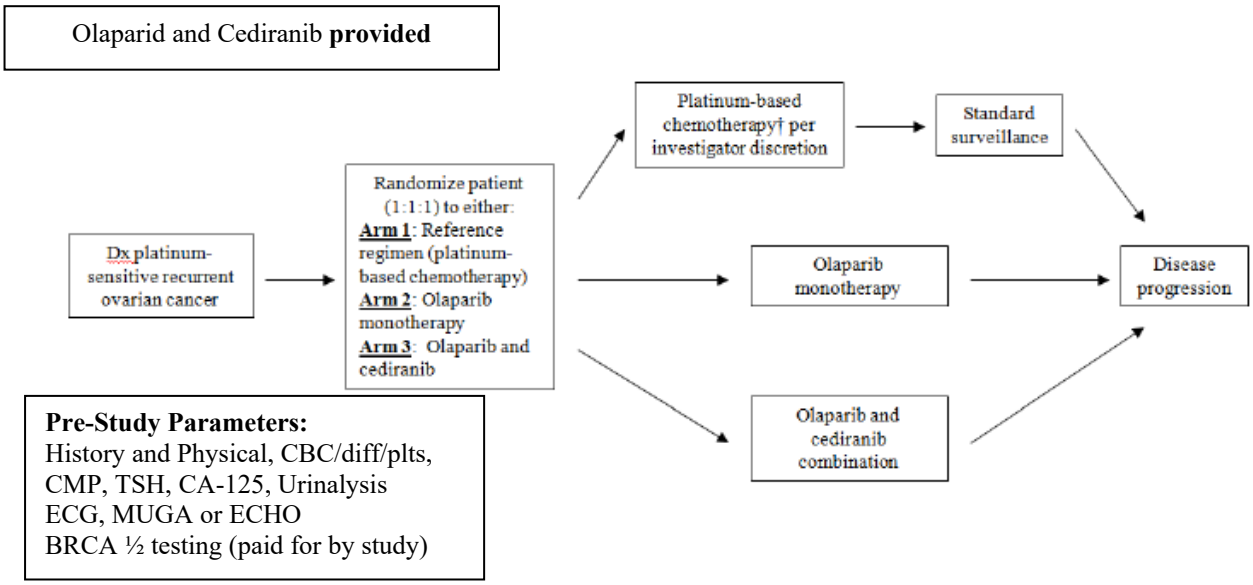
Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

Fast Facts

NRG GY004: A Phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer

SCHEMA



ELIGIBILITY CRITERIA

1. Patients must have platinum-sensitive recurrent high-grade serous or high-grade endometrioid ovarian, primary peritoneal, or fallopian tube cancers.
   Patients with other (clear cell, mixed epithelial, undifferentiated carcinoma, or transitional cell carcinoma) high-grade 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 germline BRCA testing through Myriad, Myriad testing will be accepted. If testing for germline 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 germline deleterious BRCA1 or BRCA2 mutation or BRCA rearrangement is required. Please collect a copy of Myriad or other BRCA mutational analysis (positive or VUS or negative) reports.
   a. Platinum-sensitive disease defined as no clinical or radiographic evidence of disease recurrence for > 6 months (or 182 days) after last receipt of platinum-based therapy.
   b. Patients must have had a complete clinical response to their prior line of platinum therapy and cannot have had progression through prior platinum-based therapy.
2. Patients must have signed an approved informed consent and authorization permitting release of personal health information.
3. Patients must have evaluable disease – defined as one of the following:
   a. RECIST 1.1 measurable disease OR

   b. Evaluable 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)and a CA125 that has doubled from the post-treatment nadir and is also greater than 2 times ULN.

4. Prior therapy:
   a. Prior chemotherapy must have included a first-line platinum-based regimen with or without intravenous consolidation chemotherapy.
   b. Patients may have received an unlimited number of platinum-based therapies in the recurrent setting.
   c. Patients may have received up to 1 non-platinum-based line of therapy in the recurrent setting. Prior hormonal therapy will not be considered to count as this non-platinum-based line.
   d. 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.
   e. Patients may not have previously received a PARP-inhibitor.
   f. Prior hormonal-based therapy for ovarian, primary peritoneal, or fallopian tube cancer is acceptable.
5. Patients must have an ECOG Performance Status of 0, 1 or 2 (Karnofsky ≥ 60% (See Appendix I)
6. Patients must have adequate organ and marrow function, including:
   a. Absolute neutrophil count ≥ 1,500/mcL
   b. Platelets > 100,000†/mcL
   c. Hemoglobin ≥ 10 g/dL
   d. Creatinine ≤ the institutional upper limit of normal (ULN) OR creatinine clearance ≥60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal.
   e. 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 ≤ 500mg over 24 hours.
   f. Total bilirubin ≤ 1.5x the institutional ULN
   g. AST (SGOT) and ALT (SGPT) ≤ 3 times institutional ULN.
7. Toxicities of prior therapy (excepting alopecia) should be resolved to less than or equal to Grade 1 as per NCI-CTCAE v4.0 (located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. `Patients with long-standing stable grade 2 neuropathy may be considered after discussion with the overall PI, but may not receive carboplatin and paclitaxel as the reference regimen, if randomized to that arm.
8. Patients must be able to swallow and retain oral medications and without gastrointestinal illnesses that would preclude absorption of cediranib or olaparib.
9. Patients must have adequately controlled blood pressure (BP), with a BP no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. 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 Patients with hypertension may be managed with up to a maximum of three antihypertensive medications. It is strongly recommended that patients who are on three antihypertensive medications be followed by a cardiologist or blood pressure specialist for management of blood pressure while on protocol.

10. Patients must be willing and able to check and record daily blood pressure readings. Blood pressure cuffs will be provided to patients randomized to Arm III. Please refer to section 9.7, and Appendix IX.
11. 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.
12. Adequately controlled thyroid function, with no symptoms of thyroid dysfunction and TSH within normal limits.
13. Age > 18.

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. Patients may not be receiving any other investigational agents nor have participated in an investigational trial within the past 4 weeks.
3. Patients may not be receiving any medication that may markedly affect renal function (e.g., vanocmycin, amphotericin, pentamidine).
4. Patients may not have received prior treatment affecting the VEGF pathway (including, but not limited to thalidomide, sunitinib, pazopanib, sorafenib, and nintedanib). Bevacizumab used in the upfront setting in conjunction with chemotherapy and/or as maintenance to treat newly diagnosed disease will be allowed.
5. Patients may not have previously received a PARP inhibitor.
6. CA-125 only disease without RECIST 1.1 measurable or otherwise evaluable disease as per section 3.1.3.
7. 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. Screening imaging to rule out brain metastases is not required for screening, but should be performed prior to study enrollment if clinically indicated. 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.
8. History of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib or olaparib.
9. 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 II. Strong inhibitors and inducers of UGT/PgP should be used with caution.

10. 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.
11. History of intra-abdominal abscess within the past 3 months.
12. Current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months prior to starting study drugs.
13. Dependency on IV hydration or TPN.
14. 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 lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell, or other FIGO grade 3 lesions
    d. Prior cancer treated with a curative intent with no evidence of recurrent disease 3 years following diagnosis and judged by the investigator to be at low risk of recurrence.
15. 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. NYHA classification of III or IV
16. 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
17. History of stroke or transient ischemic attack within six months
18. Any prior history of hypertensive crisis or hypertensive encephalopathy
19. Clinically significant peripheral vascular disease or vascular disease (including aortic aneurysm or aortic dissection)
20. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting cediranib
21. 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.
22. 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.

23. 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.
24. 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.
25. No features suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.
26. No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUBCT)