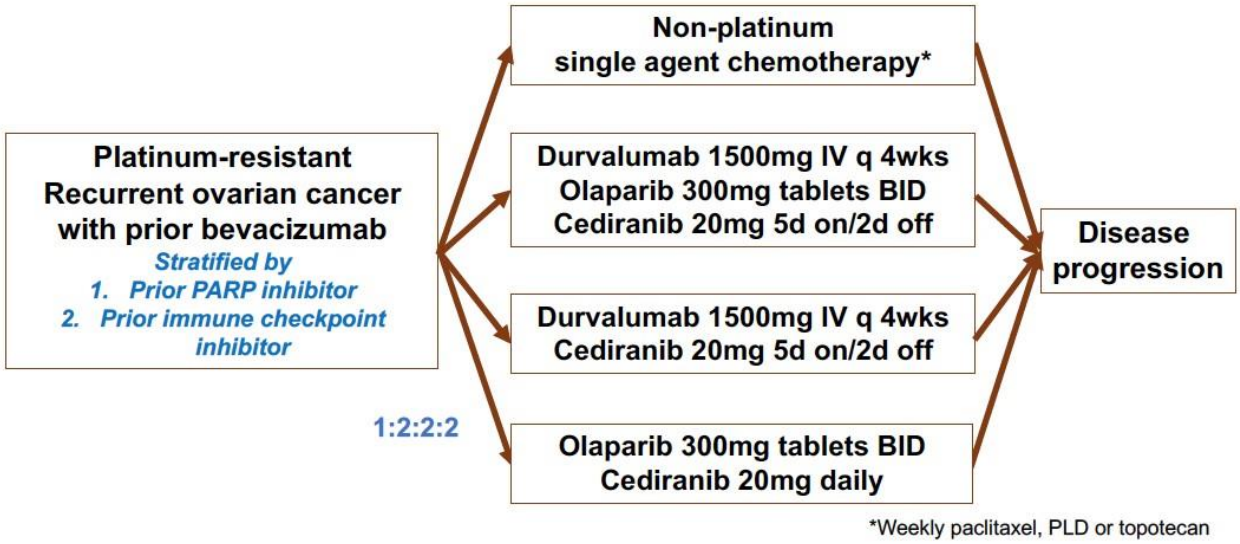
NRG-GY023
SCHEMA



*Non-platinum single agent chemotherapy includes weekly paclitaxel, topotecan or pegylated liposomal doxorubicin (PLD). There can be no deviance from the prescribed regimens, e.g. addition of bevacizumab or other agents.

Randomization is 1:2:2:2

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Women with recurrent/persistent platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers; platinum-resistant disease is defined as progression within < 6 months from completion of platinum based therapy. The date should be calculated from the last administered dose of platinum therapy.

3.1.2 Patients must have histologically or cytologically confirmed ovarian cancer, peritoneal cancer or fallopian tube cancer and must have a histological diagnosis of high grade serous, grade 3 endometrioid or clear cell carcinoma based on local histopathological findings.

Patients with low grade serous, grade 1 or 2 endometrioid, mixed epithelial, undifferentiated carcinoma, mucinous 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 required for study enrollment.

3.1.3 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 upper limit of normal (ULN)).

3.1.4 Prior therapy:

- At least two prior treatment regimens (including primary therapy) but up to 5 lines of systemic anticancer therapy. Hormonal therapy (such as tamoxifen, aromatase inhibitors) will not count as a previous treatment regimen.
- Prior use of bevacizumab in the upfront or recurrent setting ***is required.***
- Prior use of PARP inhibitor is allowed.
- Prior use of immune checkpoint blockade (e.g., a PD-L1/PD-1inhibitor or a CTLA-4 inhibitor) is allowed.

3.1.5 ECOG Performance Status of 0, 1, or 2 (see Appendix I).

3.1.6 Patients must have adequate organ and marrow function as defined below

- Absolute neutrophil count (ANC) ≥ 1,500/mcL
- Hemoglobin > 10 g/dL
- Platelets ≥ 100,000/mcL
- Creatinine ≤ 1.5 x institutional/laboratory ULN
  OR
  measured creatinine clearance > 50 mL/min/1.73 m^2
- 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
- Total serum bilirubin level ≤ 1.5 x ULN (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled)
- AST and ALT ≤ 3 x ULN

3.1.7 Age ≥ 18 years.

3.1.8 Body weight > 30 kg

3.1.9 Adequately controlled blood pressure (SBP ≤ 140; DBP ≤ 90 mmHg) on a 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 study registration. 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. BP cuffs will be provided to patients randomized to the cediranib-containing arms (Appendix X).

3.1.10 Adequately controlled thyroid dysfunction with no symptoms of thyroid dysfunction and normal TSH. If TSH is not within normal range despite no symptoms of thyroid dysfunction, normal free T4 level is required.

3.1.11 Able to swallow and retain oral medications and no GI illnesses that would preclude absorption of olaparib and cediranib as judged by treating physician.

3.1.12 Toxicities of prior therapy (excepting alopecia and vitiligo), should be resolved to less than or equal to Grade 1 as per CTCAE v5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

3.1.13 Women of childbearing potential (WOCBP) must agree to use two forms of birth control (hormonal or barrier method of birth control; abstinence).

Note: Definition of women of no longer having childbearing potential:
Postmenopausal or evidence of non-childbearing status for women of childbearing potential as confirmed by a negative urine or serum pregnancy test within 7 days prior to start of study treatment.

Postmenopausal is defined as: Age ≥60 years, or
Age <60 with any one or more of the conditions below:

- Amenorrheic for ≥1 year in the absence of chemotherapy and/or hormonal treatments,
- Luteinizing hormone and/or Follicle stimulating hormone and/or estradiol levels in the post-menopausal range,
- Radiation-induced oophorectomy with last menses >1 year ago,
- Chemotherapy-induced menopause with >1 year interval since last menses,
- Surgical sterilization (bilateral oophorectomy or hysterectomy).

3.1.14 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and authorization permitting release of personal health information.

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.2.1. Primary platinum-refractory disease defined as progression during first-line platinum-based chemotherapy.

3.2.2 Rising CA-125 only without RECIST 1.1 evaluable disease.

3.2.3 Prior therapy:

- Patients who have had chemotherapy, investigational drugs or radiotherapy within 3 weeks prior to study registration or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier.
- Patients may not have had hormonal therapy within 2 weeks of study registration. Patients receiving raloxifene for bone health as per FDA indication may remain on raloxifene absent other drug interactions.
- Prior use of concurrent olaparib and cediranib combination.
- Patients who have had prior PARP inhibitor or immune checkpoint blockade requiring dose modifications as they cannot start this study at full dose.

3.2.4 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 3 months prior to study registration.

3.2.5 Current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months of study registration except temporary (<24hr) improved with medical management, within last 3 months.

3.2.6 Any prior grade ≥ 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE > grade 1.

3.2.7 Dependency on IV hydration or TPN.

3.2.8 Pregnant women. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with these drugs, breastfeeding should be discontinued. These potential risks may also apply to other agents used in this study.

3.2.9 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.

3.2.10 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 registration.

3.2.11 Patients who have the following clinical conditions are considered to be at increased risk for cardiac toxicities. Patients with any cardiac history of the following conditions:

- History of myocardial infarction or myocarditis within six months of study registration
- Unstable angina
- Resting ECG with clinically significant abnormal findings.
- New York Heart Association functional classification of III or IV (Appendix II)

3.2.12 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:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab or T-DM1
- Prior central thoracic radiation therapy (RT), including RT to the heart
- History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)
- Prior history of impaired cardiac function

3.2.13 History of stroke or transient ischemic attack within six months of study registration.

3.2.14 Clinically significant peripheral vascular disease or vascular disease (aortic aneurysm or aortic dissection).

3.2.15 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study treatment. Patients must have recovered from any effects of any major surgery and surgical wound should have healed prior to starting treatment.
Note: Local surgery of isolated lesions for palliative intent is acceptable.

3.2.16 Evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events, including warfarin, is permitted. Patients receiving warfarin are recommended to have careful monitoring of international normalized ratio (INR), as detailed in Section 4 and Section 9.

3.2.17 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).

3.2.18 Human Immunodeficiency Virus (HIV) positive patients due to potential drug and drug interactions

3.2.19 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.

3.2.20 Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment.

Note: Patients, if enrolled, should not receive live vaccine whilst receiving study treatment and up to 30 days after the last dose of study treatment.

3.2.21 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.

3.2.22 Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A4. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

3.2.23 Current or prior use of immunosuppressive medication within 14 days of study registration. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (*e.g.*, intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (*e.g.*, CT scan premedication)

3.2.24 History of allergic reactions attributed to compounds of similar chemical or biologic composition to durvalumab, olaparib, or cediranib.

3.2.25 Patients with active autoimmune disease that has required systemic treatment in the past 2 years (*i.e.*, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (*e.g.*, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.26 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), or hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.