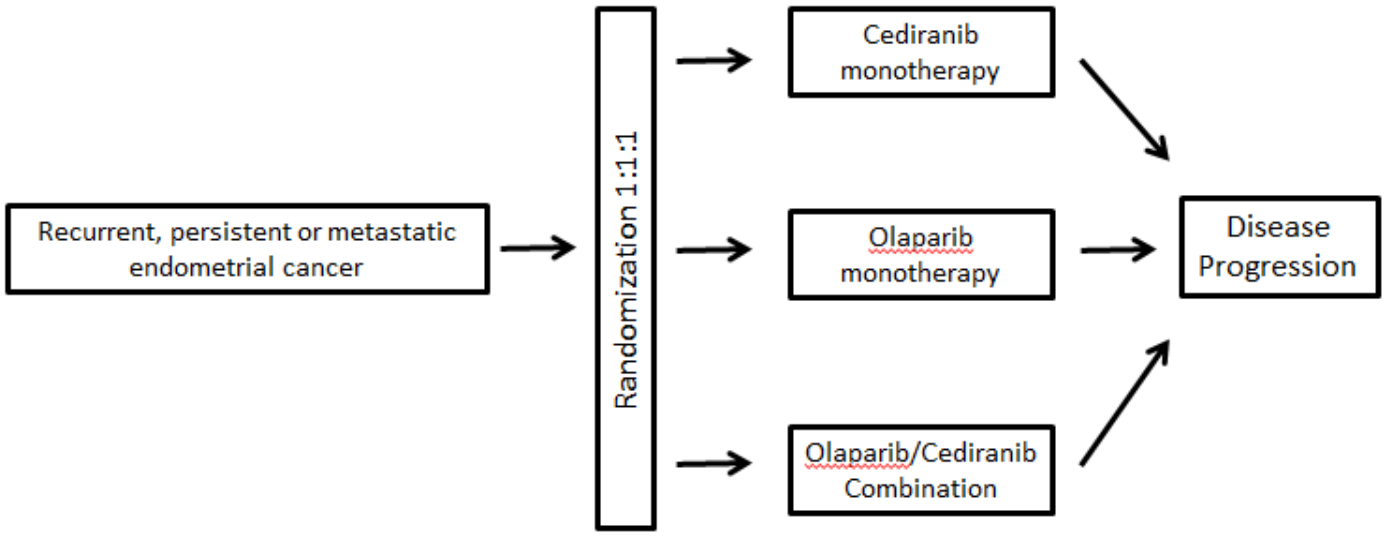
NRG-GY012 SCHEMA



* additional arms may be added by protocol amendment

3.1.1 Patients must have recurrent or persistent endometrial carcinoma, which is refractory to curative therapy or established treatments. Histologic confirmation of the original primary tumor is required.

Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.). NOTE: Clear cell and carcinosarcoma histology is excluded.

3.1.2 Patients must have measurable disease as defined by RECIST 1.1 or non-measurable (detectable) disease.

3.1.2.1 Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI (See section 14). Patients with measurable disease must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST version 1.1 (Section 14). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.1.2.2 Non-measurable (detectable) disease in a patient is defined in this protocol as one who does not have measurable disease but has at least one of the following conditions:

- Ascites and/or pleural effusion attributed to tumor;
- Solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 (see Section 14) definitions for target lesions.

3.1.3 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.1.4 Prior Therapy:

3.1.4.1 Patients must have had one prior chemotherapeutic regimen for management of endometrial carcinoma. Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.

3.1.4.2 Patients are allowed to receive, but are not required to receive, one additional cytotoxic regimen for management of recurrent or persistent disease according to the following definition: Cytotoxic regimens include

any agent that targets the genetic and/or mitotic apparatus of dividing cells, resulting in dose-limiting toxicity to the bone marrow and/or gastrointestinal mucosa. Note: Patients on this non-cytotoxic study are allowed to receive one additional cytotoxic chemotherapy regimen for management of recurrent or persistent disease, as defined above. However, due to the novel nature of biologic compounds, patients are encouraged to enroll on second-line non-cytotoxic studies prior to receiving additional cytotoxic therapy.

3.1.4.3 Patients may have received non cytotoxic therapy including immunotherapy but excluding cediranib and olaparib for management of recurrent or persistent disease. Prior hormonal therapy is allowed. Hormonal therapy for grade 1 endometrial cancers with low volume or indolent disease is encouraged.

3.1.5 Age $\geq$ 18;

3.1.6 The trial is open to females only (including women with an intact uterus with uterine cancer). Fertile females of childbearing potential need to agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation, and have a negative serum or urine pregnancy test within 3 days prior to the start of study treatment.

3.1.7 Patients must have an ECOG Performance Status of 0, 1 or 2 (Karnofsky $\geq$ 60%) within 7 days prior to registration;

3.1.8 Patients must have adequate organ and marrow function measured within 28 days prior to administration of study drug including;

3.1.8.1 Hemoglobin (Hgb) $\geq$ 10 g/dL with no blood transfusion in the past 28 days

3.1.8.2 Platelet count $\geq$ 100 x 10^9/L

3.1.8.3 ANC $\geq$ 1.5 x 10^9/L

3.1.8.4 Creatinine clearance $\geq$ 51 mL/min/

3.1.8.5 Serum bilirubin $\leq$ 1.5 X ULN.

3.1.8.6 Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) $\leq$ 3 x ULN

3.1.8.7 Urine protein: creatinine (UPC) <1 or < 2+ proteinuria on two consecutive dipsticks taken no less than 1 week apart. Patients with 2+

proteinuria on dipstick must also have UPC < 0.5 on 2 consecutive samples.

3.1.9 Patients must be able to swallow and retain oral medications and without gastrointestinal illnesses that would preclude absorption of cediranib or olaparib.

3.1.10 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.

3.1.10.1 Patients must be willing and able to check and record daily blood pressure readings.

3.1.11 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.1.12 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction.

3.1.13 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 IPs. 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 Patients must have a life expectancy of greater than 16 weeks.

3.2 Ineligibility Criteria

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

3.2.1 Prior enrollment into a clinical trial including cediranib or olaparib. Note: prior bevacizumab is not an exclusion criterion.

3.2.2 Prior chemotherapy, endocrine therapy, radiotherapy, or investigational agents within 4 weeks.

3.2.3 Current signs/symptoms of bowel obstruction and/or signs/symptoms of bowel obstruction within the preceding 3 months.

3.2.4 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.

3.2.5 Uncontrolled intercurrent illness including, but not limited to known ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Concomitant use of known strong cytochrome (CYP) 3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatments is 2 weeks for strong inhibitors, and at least 1 week for moderate inhibitors. See Appendix VIII**.**

3.2.7 Concomitant use of known strong CYP3A inducers (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting study treatments is 5 weeks for enzalutamide or phenobarbital and 4 weeks for other agents.

3.2.8 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. For women of child bearing capacity a negative pregnancy test is required.

3.2.9 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.

3.2.10 Known active Hepatitis B or Hepatitis C infection on antiviral treatment"

3.2.11 Prior history of stroke or transient ischemic attack within the last 6 months

3.2.12 Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines, for patients with the following risk factors:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior central thoracic RT, including exposure of heart to therapeutic doses of ionizing RT
- History of myocardial infarction within 6-12 months prior to start of IPs
- Prior history of other significant impaired cardiac function

3.2.13 Patients with any of the following:

- History of myocardial infarction within 6 months prior to starting treatment
- Unstable angina
- Resting electrocardiogram (ECG) with clinically significant abnormal findings or with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
- New York Heart Association functional classification of III or IV.

3.2.14 Prior history of hypertensive crisis or hypertensive encephalopathy

3.2.15 Major surgical procedure within 2 weeks prior to starting treatment; patients must have recovered from any effects of any major surgery and surgical wound should have healed prior to starting treatment

3.2.16 History of intra-abdominal abscess within 3 months prior to starting treatment

3.2.17 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.

3.2.18 No prior allogeneic bone marrow transplant or double umbilical cord blood

transplantation (dUBCT)

3.2.19 Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable

3.2.20 Patients with myelodysplastic syndrome (MDS)/treatment-related acute myeloid leukemia (t-AML) or with features suggestive of MDS/AML

3.2.21 Central nervous system metastases:

- Symptomatic uncontrolled brain metastases requiring corticosteroid treatment. History of spinal cord compression unless after definitive treatment the patient has clinically stable disease (SD) for at least 28 days prior to starting IPs. In the absence of these features and in an asymptomatic patient a scan to confirm the absence of brain metastases is not required.

3.2.22 Other malignancy within the last 5 years except for:

- Curatively treated basal cell or squamous cell carcinoma of skin; in situ cancer of the cervix, ductal carcinoma in situ of the breast or stage 1, grade 1 endometrial carcinoma.

- Curatively treated other solid tumors including lymphomas (without bone marrow involvement) with no evidence of disease for ≥5 years prior to start of IPs.

3.2.23 Persisting ≥Grade 2 CTCAE toxicity (except alopecia and Grade 2 peripheral neuropathy) from previous anti-cancer treatment(s).

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