NRG-GY036
SCHEMA

FIGO stage III-IV fallopian tube, ovarian, or primary peritoneal cancer with pathogenic *BRCA1/2* mutation (germline or somatic) or homologous recombination deficiency (HRD) after response to initial platinum-based chemotherapy

STEP 1 REGISTRATION

STRATIFY

- BRCA deleterious alteration vs. BRCA Wildtype AND HRD+
- +/- Bevacizumab (physician's choice)
- Response to platinum-based therapy (PR vs. CR)

RANDOMIZE 1:1

Arm 1	**Arm 2**
Olaparib 300mg twice daily for TWO years^ +/-Bevacizumab*	Olaparib 300mg twice daily for ONE year^ +/-Bevacizumab*

^See section 5.1 for more detailed treatment plan
*Cycle length is 21 days. Bevacizumab (reference product or biosimilar) treatment will be stopped at the completion of the first year of treatment in both arms.

3. ELIGIBILITY CRITERIA

3.1 On Study Guidelines

Physicians should consider the following when evaluating if the patient is appropriate for this protocol. [HIV, HBV, and HCV testing do not need to be performed as part of the study; the below language provides guidelines for inclusivity of patients with known HIV, HBV, and/or HCV infection]:

- For patients with known HIV, HBV, and/or HCV infection:
  - HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
  - For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
  - 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.
- 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.

In addition:

- The effects of Olaparib and bevacizumab on the developing human fetus are unknown. For this reason and because these agents are known to be teratogenic, participants of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) during study therapy and for 6 months following the completion of study therapy. Should a participant become pregnant or suspect pregnancy while participating in this study, they should inform their treating physician immediately.

Note: Per NCI guidelines, exceptions to eligibility criteria are not permitted. For questions concerning eligibility, see protocol cover page.

NIH Participant Population Inclusion Policy

NIH policy requires that participants regardless of gender identity and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Participants of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.2 Eligibility Criteria

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

3.2.1 Documentation of Disease

Patients with newly diagnosed, pathologically confirmed, FIGO Stage III or IV ovarian cancer of the following types:

- high grade serous,
- high grade endometrioid, and/or
- other epithelial ovarian cancer with *BRCA1/2* deleterious alteration (germline or somatic).

Submission of pathology report is required
Ovarian cancer = ovarian, fallopian, or primary peritoneal cancer.

Patients must have:

1) Documented variant (tumor or germline) in *BRCA1* or *BRCA2* that is predicted to be pathogenic or suspected pathogenic (deleterious alteration).
   - Submission of testing report is required.

OR

2) *BRCA 1/2* wildtype AND known HRD deficient tumor determined by any commercial or academic, CLIA-certified laboratory (e.g., Myriad MyChoice©)
   - Submission of testing report is required.

3.2.2 Prior Treatment

Patient must have undergone cytoreductive surgery (primary or interval).

Patients must have completed first line platinum-based therapy prior to registration:

- Platinum based chemotherapy course must have consisted of a minimum of 4 treatment cycles and a maximum of 9, although it is strongly recommended that patients receive at least 6 cycles unless medically contraindicated.
    - For those receiving less than 6 cycles of platinum-based therapy, the reason for this must be documented and could include hematologic toxicity or non-hematologic toxicities directly related to therapy.
- Intravenous, intraperitoneal, or neoadjuvant platinum-based chemotherapy is allowed; for weekly therapy, three weeks are considered one cycle.
- Patients must not have received an investigational agent during their first line course of chemotherapy.

Patients must have, in the opinion of the investigator, no clinical evidence of disease progression following completion of this chemotherapy course (partial or complete response to platinum-based chemotherapy).

Patients with treated brain metastases are eligible if follow up brain imaging after CNS directed therapy shows no evidence of progression and patients are neurologically stable off steroid therapy.

Patients must be randomized at least 3 weeks and no more than 12 weeks after their last dose of chemotherapy (last dose is the day of the last infusion of platinum agent).

No previous treatment with a PARP inhibitor, including olaparib, niraparib, and rucaparib.

3.2.3 Age ≥ 18

3.2.4 ECOG Performance Status of ≤ 2

See Appendix I for performance criteria.

3.2.5 Not Pregnant and Not Nursing

3.2.6 Required Organ Function

Adequate hematologic function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 9 g/dl

Adequate renal function defined as follows:

- Creatinine clearance (CrCL) of >30 mL/min by the Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{creatinine (mg / dL)}} \quad (\times 0.85 \text{ for female patients})$$

Adequate hepatic function defined as follows:

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) (patients with

known Gilbert's disease who have bilirubin level ≤ 3 x institutional ULN may be enrolled)
- AST and ALT ≤3 x institutional ULN

Adequate cardiac function defined as follows:
- 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. To be eligible for this trial, patients should be class 2B or better (see Appendix II: New York Heart Association (NYHA) Functional Classification)

3.2.7 Comorbid Conditions
- No active infection requiring parental antibiotic(s).
- No current evidence of intra-abdominal abscess, abdominal/pelvic fistula (not diverted), gastrointestinal perforation, GI obstruction, and/or need for drainage nasogastric or gastrostomy tube.
- No current inability to swallow orally administered medication.
- No history of myelodysplastic syndrome and/or acute myeloid leukemia.
- No history of allogeneic bone marrow transplant.

3.2.8 Concomitant Medications
No concomitant use of strong or moderate CYP3A inducers.

3.2.9 Allergies
No known hypersensitivity to olaparib or any of the excipients of the product.