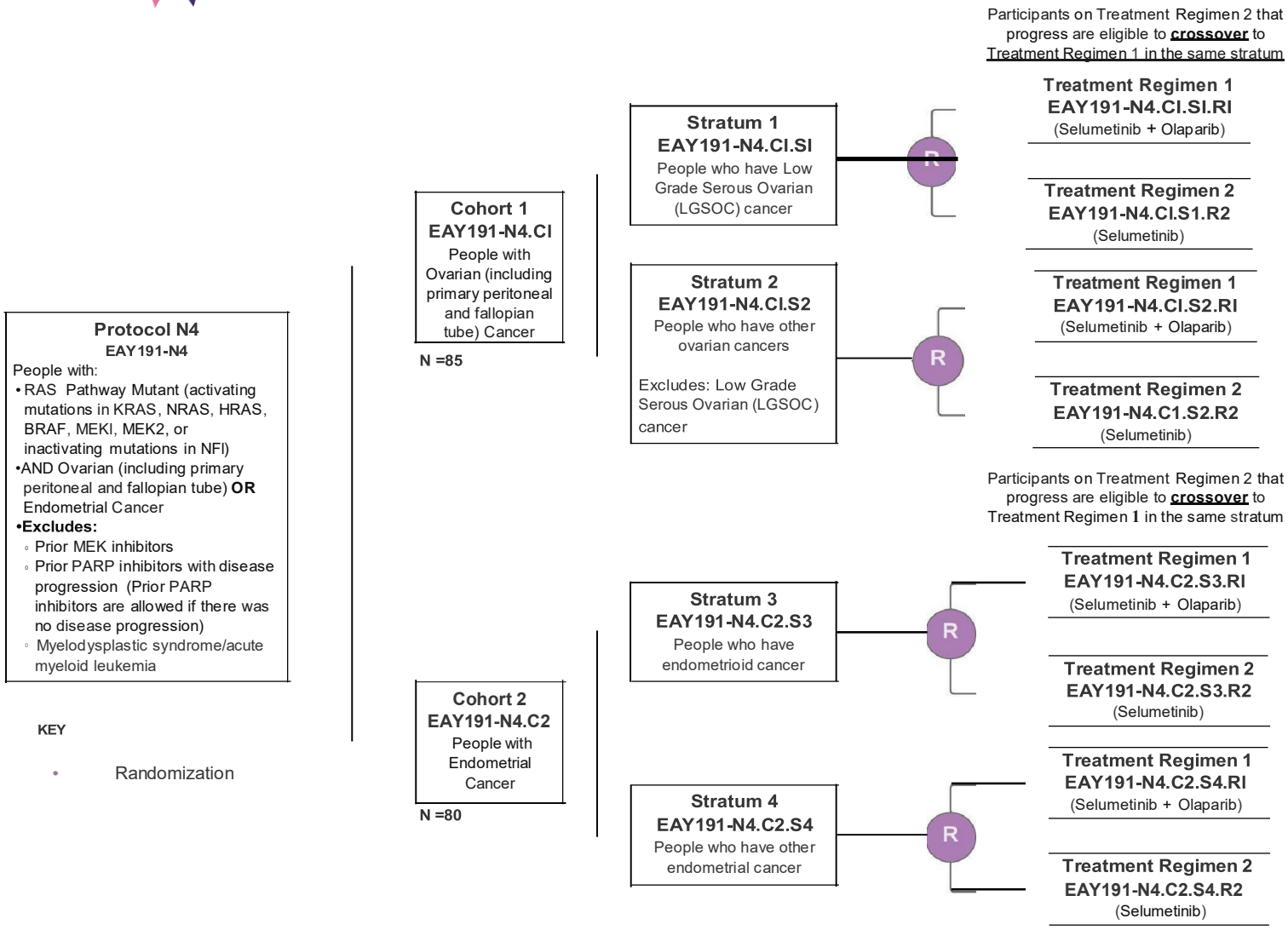
SCHEMA


Protocol N4
EAY191-N4
People with:
• RAS Pathway Mutant (activating mutations in KRAS, NRAS, HRAS, BRAF, MEKI, MEK2, or inactivating mutations in NFI)
•AND Ovarian (including primary peritoneal and fallopian tube) OR Endometrial Cancer
•Excludes:
◦ Prior MEK inhibitors
◦ Prior PARP inhibitors with disease progression (Prior PARP inhibitors are allowed if there was no disease progression)
◦ Myelodysplastic syndrome/acute myeloid leukemia
KEY
• Randomization
Cohort 1
EAY191-N4.CI
People with Ovarian (including primary peritoneal and fallopian tube) Cancer
N =85
Cohort 2
EAY191-N4.C2
People with Endometrial Cancer
N =80
Stratum 1
EAY191-N4.CI.SI
People who have Low Grade Serous Ovarian (LGSOC) cancer
Stratum 2
EAY191-N4.CI.S2
People who have other ovarian cancers
Excludes: Low Grade Serous Ovarian (LGSOC) cancer
Stratum 3
EAY191-N4.C2.S3
People who have endometrioid cancer
Stratum 4
EAY191-N4.C2.S4
People who have other endometrial cancer
R
Participants on Treatment Regimen 2 that progress are eligible to crossover to Treatment Regimen 1 in the same stratum
Treatment Regimen 1
EAY191-N4.CI.SI.RI
(Selumetinib + Olaparib)
Treatment Regimen 2
EAY191-N4.CI.S1.R2
(Selumetinib)
Treatment Regimen 1
EAY191-N4.CI.S2.RI
(Selumetinib + Olaparib)
Treatment Regimen 2
EAY191-N4.C1.S2.R2
(Selumetinib)
Participants on Treatment Regimen 2 that progress are eligible to crossover to Treatment Regimen 1 in the same stratum
Treatment Regimen 1
EAY191-N4.C2.S3.RI
(Selumetinib + Olaparib)
Treatment Regimen 2
EAY191-N4.C2.S3.R2
(Selumetinib)
Treatment Regimen 1
EAY191-N4.C2.S4.RI
(Selumetinib + Olaparib)
Treatment Regimen 2
EAY191-N4.C2.S4.R2
(Selumetinib)

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please 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 Patients must be enrolled on the ComboMATCH Master Registration Trial EAY191.

3.1.2 Patients must have RAS pathway mutations as determined by the ComboMATCH screening assessment.

Cohort 1: Patients with histologically confirmed RAS pathway mutant ovarian, primary peritoneal, or fallopian tube ("ovarian") cancer (activating mutations in KRAS, NRAS, HRAS, BRAF, MEK1, MEK2, or inactivating mutations in NF1).

Cohort 2: Patients with histologically confirmed RAS pathway mutant endometrial cancer (activating mutations in KRAS, NRAS, HRAS, BRAF, MEK1, MEK2, or inactivating mutations in NF1).

3.1.3 Patients must have disease that can be safely biopsied and agree to a pre-treatment biopsy or, if disease cannot be safely biopsied, have archival tissue available from within 12 months prior to the date of registration on the ComboMATCH Registration Trial (EAY191).

3.1.4 Patients must have progressed after first-line treatment for recurrent or persistent disease.

3.1.5 Patients with ovarian cancer should not be eligible for further platinum-based therapy.

3.1.6 Patients with endometrial cancer must have received or been offered an immune oncology agent (alone or in combination with lenvatinib) unless there are existing contraindications for immune oncology agents or lenvatinib.

3.1.7 Patients may have received unlimited prior therapy.

3.1.8 Patients must have measurable and biopsiable disease. Measurable disease is defined by RECIST 1.1 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 12).

Patients must have at least one "target lesion" separate from the lesion to be biopsied to be used to assess response on this protocol as defined by RECIST version 1.1. 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.

3.1.9 Prior therapy must have been completed at least four weeks prior to registration.

3.1.10 Age ≥ 18.

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

3.1.12 Adequate hematologic function within 14 days prior to registration defined as follows:

- Hemoglobin (Hgb) ≥ 9.5 g/dL with no blood transfusion in the past 28 days
- Platelets ≥ 100,000/mcl
- Absolute neutrophil count (ANC) ≥ 1,500/mcl

3.1.13 Adequate renal function within 14 days prior to registration defined as follows:

Patients must have creatinine clearance estimated of ≥50 mL/min using the Cockcroft-Gault equation or based on a 24 hour urine test:

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

(14-JUN-2023)

3.1.14 Adequate hepatic function within 14 days prior to registration defined as follows:

- Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN) or ≤ 3 x ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia)
- AST and ALT ≤ 3 x ULN

(14-JUN-2023)

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

3.1.16 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.)

3.1.17 Women of childbearing potential (WOCBP) must agree to use two forms of birth control (hormonal or barrier method of birth control; abstinence) during the study and for 12 weeks after completing treatment. See Appendix III.

Non-sterilized male partners of WOCBP (including males sterilized by a method other than bilateral orchidectomy eg, vasectomy) who intend to be sexually active with a female partner must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and the drug washout period (at least

16 weeks after the last dose of study intervention) to prevent pregnancy in a partner. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Vasectomized (i.e., sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

3.1.18 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.

3.1.19 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial.

3.1.20 Patients with evidence of chronic hepatitis B virus (HBV) infection must have an undetectable HBV viral load 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.

3.1.21 Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression.

Extra caution should be taken with olaparib, as it crosses the blood brain barrier and can cause edema in brain metastases.

3.1.22 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., 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 Patients who have received any MEK inhibitors.

3.2.2 Patients who have progressed while receiving a PARP inhibitor.

3.2.3 Patients who have received chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to registration.

3.2.4 Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e., have residual toxicities > Grade 1) with the exception of alopecia.

3.2.5 Patients with uncontrolled intercurrent illness.

3.2.6 Patients with ≥ Grade 2 neuropathy within 14 days of registration.

3.2.7 Patients with severe (Child-Pugh C) liver dysfunction (See Appendix IV).

3.2.8 Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib and selumetinib or any excipients thereof.

3.2.9 Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

Supplementation with vitamin E greater than 100% of the daily recommended dose. Any multivitamin containing vitamin E must be stopped prior to study enrollment even if less than 100% of the daily recommended dosing for vitamin E.

Vitamin E must not be taken in the 7 days prior to initiation of treatment with selumetinib.

3.2.10 Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or known moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, Fluconazole, verapamil). The required washout period prior to starting olaparib is at least 14 days or 5 half-lives (whichever is longer) before the first dose of study medication.

3.2.11 Concomitant use of strong CYP2C19 inhibitors (e.g., ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole). The required washout period prior to starting selumetinib is at least 14 days or 5 half-lives (whichever is longer) before the first dose of study medication.

3.2.12 Have received or are receiving an investigational medicinal product (IMP) or other systemic anti-cancer treatment (including chemotherapy, immunotherapy, targeted therapy, biologic therapy, tumor embolization, or monoclonal antibodies) within 4 weeks prior to registration, or within a period during which the IMP or systemic target treatment has not been cleared from the body (e.g., a period of 5 'half-lives'), whichever is longer.

3.2.13 Known myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.

3.2.14 Patients who have had previous organ transplant, allogenic bone marrow transplant or double umbilical cord blood transplantation.

3.2.15 Patients who have had whole blood transfusion within 28 days prior to registration.

3.2.16 Patients with ophthalmological conditions as follows:

- Current or past history of retinal pigment epithelial detachment/central serous retinopathy or retinal vein occlusion.
- Intraocular pressure >21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP). Subjects with known glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) and are not experiencing pain related to the glaucoma, may be eligible after discussion with the Study Chair.
- Patients with any other significant abnormality on ophthalmic examination should be discussed with the Study Chair for potential eligibility.
- Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or longstanding orbito-temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study.

3.2.17 Patients with severe, active co-morbidity defined as any of the following: **(21-APR-2023)**

- History of confirmed pneumonitis
- Uncontrolled hypertension (BP ≥ 150/90 mmHg despite medical therapy)
- Acute coronary syndrome within 6 months prior to registration
- Uncontrolled atrial fibrillation
- Known family history of long QT syndrome

3.2.18 Women who are pregnant or unwilling to discontinue nursing.

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. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf