FAST FACTS

ELIGIBILITY CRITERIA

1. Documentation of Disease:
   Histologically confirmed cancer for each cohort for which curable treatment modalities are not an option (see Section 3.2.3).

   Rare BRAF fusions and non-BRAF V600E aMOIs are acceptable.

2. Measurable disease as defined in Section 11.0.

   Measurable disease per RECIST 1.1. There is a mandatory baseline biopsy for all ComboMATCH studies. Hence, patient must have a biopsiable lesion at baseline. Of note, in the case when a baseline biopsy is done after scans are obtained, a lesion separate from one that is biopsied needs to be measurable per RECIST 1.1. All radiologic studies must be performed within 28 days prior to randomization.

3. Cohort Specific Eligibility

   Cohort 1
   - Low grade serous ovarian cancer with *KRAS, NRAS, non-BRAF V600E aMOIs or rare RAF fusions are acceptable.*
   - No prior MEK inhibitor or CDK4/6 inhibitor therapy.
   - Any number of prior therapies permitted.
   - No major surgery within 4 weeks (excluding placement of vascular access), minor surgery within 2 weeks, or palliative radiotherapy within 2 weeks of the first dose of study therapy.
   - No prior cancer-directed therapy within 28 days prior to registration. Patients may have received cancer-directed hormonal therapy up to 14 days prior to the start of study treatment.

Cohort 2

- Low grade serous ovarian cancer.

- Prior progression of disease on a MEK inhibitor (prior binimetinib permitted).

- If patient has previously received binimetinib, they cannot have required dose reduction or discontinuation of binimetinib due to adverse events.

- No prior receipt of a CDK4/6 inhibitor.

- No major surgery within 4 weeks (excluding placement of vascular access), minor surgery within 2 weeks, or palliative radiotherapy within 2 weeks of the first dose of study therapy.

- No prior cancer-directed therapy within 28 days prior to registration. Patients may have received cancer-directed hormonal therapy up to 14 days prior to the start of study treatment. Patients migrating from Cohort 1 may have received binimetinib within 28 days of registering to Cohort 2.

Cohort 3

- Pancreatic cancer with KRAS/NRAS/HRAS, non-BRAF V600E aMOIs or rare RAF fusions are acceptable.

- No prior MEKi and CDK4/6i therapy.

- Progression after at least one line of prior therapy as long as there is no standard therapy available or acceptable to patients that is thought to be of benefit.

- Any number of prior therapies are permitted.

- No major surgery within 4 weeks (excluding placement of vascular access), minor surgery within 2 weeks, or palliative radiotherapy within 2 weeks of the first dose of study therapy.

- No prior cancer-directed therapy within 28 days prior to registration. Patients may have received cancer-directed hormonal therapy up to 14 days prior to the start of study treatment

Cohort 4

- KRAS/NRAS/HRAS, non-BRAF V600E aMOIs or rare RAF fusions are acceptable.

- No prior MEKi and CDK4/6i therapy and progression after at least one line of prior therapy, as long as there is no standard therapy available or acceptable to patients that is thought to be of benefit.

- Any number of prior therapies are permitted.

- No more than 6 patients with a given tumor type allowed in this cohort.

- Any tumor type, except: GSOC/NSCLC/CRC/pancreatic/melanoma.

- No major surgery within 4 weeks (excluding placement of vascular access), minor surgery within 2 weeks, or palliative radiotherapy within 2 weeks of the first dose of study therapy.

- No prior cancer-directed therapy within 28 days prior to registration. Patients may have received cancer-directed hormonal therapy up to 14 days prior to the start of study treatment.

4. **Not pregnant and not nursing**, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

   Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required

5. **Age ≥ 18 years**

6. **ECOG Performance Status <2**

7. **Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/ mm3
Platelet Count	≥ 100,000/mm3
Hemoglobin	> 9 g/dL
Creatinine or Calc. Creatinine Clearance	≤ 1.5 x upper limit of normal (ULN) ≥ 30 mL/min as calculated by the Cockcroft-Gault formula
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN). Patients with Gilbert syndrome may enroll if total bili <3 mg/dL (51 micromole/L)
AST / ALT Creatine Phosphokinase	≤ 2.5 x upper limit of normal (ULN) CPK ≤ 2.5 x ULN

8. **Patients must be able to swallow oral formulations of the agents**

9. **Comorbid conditions**

- No history of interstitial lung disease. No history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.

  - Patients should not have history of bowel perforation or intestinal

fistulas in the last 6 months.

- No patients with the inability to swallow oral medications or impaired gastrointestinal absorption due to gastrectomy or active inflammatory bowel disease.

- No active skin disorder that has required systemic therapy within the past 1 year.

- No history of rhabdomyolysis.

- No concurrent ocular disorders including:

    o Subjects with history of glaucoma, history of retinal vein occlusion (RVO), predisposing factors for RVO, including uncontrolled hypertension, uncontrolled diabetes.

    o Subject with history of retinal pathology or evidence of visible retinal pathology that is considered a risk factor for RVO, intraocular pressure > 21 mm Hg as measured by tonometry, or other significant ocular pathology, such as anatomical abnormalities that increase the risk for RVO.

    o Subjects with a history of corneal erosion (instability of corneal epithelium), corneal degeneration, active or recurrent keratitis, and other forms of serious ocular surface inflammatory conditions

- No patients with a history of hypersensitivity to any of the study drug(s).

- No prior allogeneic stem cell or solid organ transplantation.

- CNS metastases must have been treated with local therapy (surgery, radiation, ablation) and patient off of systemic steroids, and brain metastases stable for at least 1 month.

- No residual CTCAE ≥ Grade 2 toxicity from any prior anticancer therapy, with the exception of Grade 2 alopecia or Grade 2 neuropathy.

- Patients must not have Grade 2 neuropathy or greater, within 14 days prior to registration.

- 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 whose LVEF has been evaluated by ECHO/MUGA are excluded if the most recent exam shows an LVEF <50%

10. Concomitant medications

- Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for

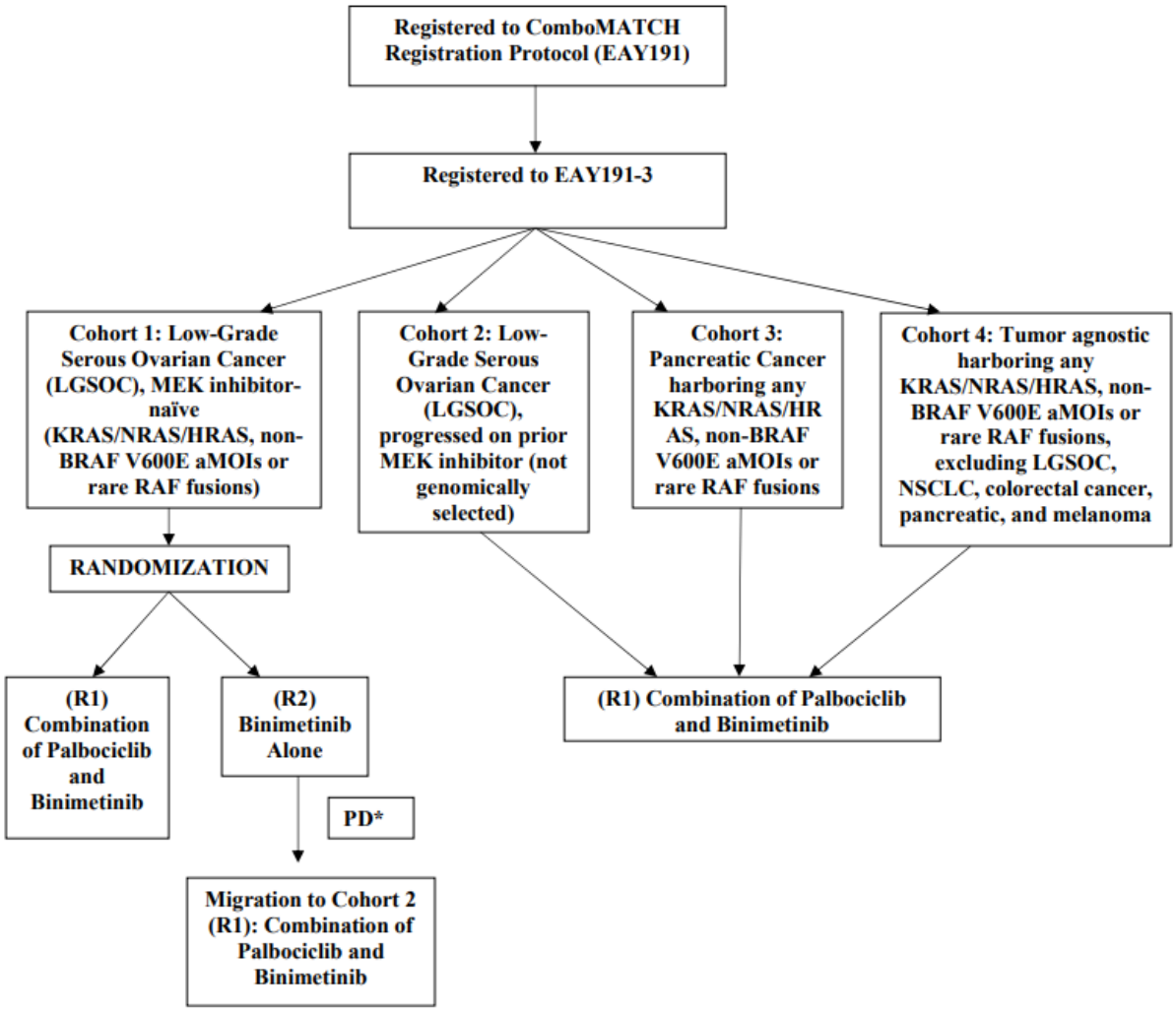
- 14 days prior to registration on the study. For additional guidance see https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-anddrug-interactions-table-substrates-inhibitors-and-inducers

- Chronic concomitant treatment with strong CYP3A4 inducers is not allowed.

- Patients must discontinue the drug 14 days prior to the start of study treatment.

- For additional guidance see https://www.fda.gov/drugs/drug-interactionslabeling/drug-development-and-drug-interactions-table-substrates-inhibitors-andinducers

- No exposure to P-glycoprotein (P-gp) inhibitors or inducers within 14 days prior to the first dose and during the course of therapy.


Registered to ComboMATCH Registration Protocol (EAY191)
Registered to EAY191-3
Cohort 1: Low-Grade Serous Ovarian Cancer (LGSOC), MEK inhibitor-naïve (KRAS/NRAS/HRAS, non-BRAF V600E aMOIs or rare RAF fusions)
Cohort 2: Low-Grade Serous Ovarian Cancer (LGSOC), progressed on prior MEK inhibitor (not genomically selected)
Cohort 3: Pancreatic Cancer harboring any KRAS/NRAS/HRAS, non-BRAF V600E aMOIs or rare RAF fusions
Cohort 4: Tumor agnostic harboring any KRAS/NRAS/HRAS, non-BRAF V600E aMOIs or rare RAF fusions, excluding LGSOC, NSCLC, colorectal cancer, pancreatic, and melanoma
RANDOMIZATION
(R1) Combination of Palbociclib and Binimetinib
(R2) Binimetinib Alone
PD*
Migration to Cohort 2 (R1): Combination of Palbociclib and Binimetinib
(R1) Combination of Palbociclib and Binimetinib