Study Rationale

- As LGS carcinoma has a high frequency of BRAF and KRAS mutations, validating that the RAS/RAF/MEK/ERK pathway is warranted in patients with these tumors.
- A Phase 2 study evaluating the MEK inhibitor selumetinib was conducted by the Gynecologic Oncology Group (GOG) in 52 patients with recurrent LGS ovarian or peritoneal carcinoma.14
- An ORR of 15%, a clinical benefit rate of 81% and a median progression-free survival (PFS) of 11 months was observed.
- Despite these patients being heavily pretreated, with 58% having received 3 or more prior therapies, both the reported ORR and the median PFS are greater than that observed for both cytotoxic chemotherapy and hormonal therapy.

Study Endpoints

**Primary**
- PFS per BICR

**Secondary**
- Overall survival
- ORR as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1
- Duration of response
- Disease control rate (best response of complete response or partial response, or stable disease documented ≥ 2 Week)
- Safety
- Patient-reported outcomes
- Pharmacokinetics of binimetinib

**Exploratory**
- Mutational status of patient tumors in RAS/RAF and other genes

**Key Inclusion Criteria**
- Female ≥ 18 years of age.
- Diagnosis of LGS of the ovary, fallopian tube or primary peritoneum, confirmed histologically and verified by central pathology review, using archival or fresh tumor tissue. Recurrent or persistent disease that has progressed (defined as radiological and/or clinical progression; an increase in CA-125 alone is not sufficient) on or after last therapy (i.e., chemotherapy, hormonal therapy, surgery) and is not amenable to potentially curative intent surgery, as determined by the treating physician.
- Must have received ≥ 1 prior platinum-based chemotherapy regimen but ≤ 3 prior chemotherapy regimens, with no limit to the number of lines of prior hormonal therapy.
- Measurable disease, as defined by RECIST V1.1, per BICR.
- Suitable for treatment with at least one of the physician’s choice chemotherapy options.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

**Key Exclusion Criteria**
- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).
- Prior therapy with a MEK inhibitor or BRAF inhibitor.
- History of Gilbert’s syndrome.
- Impaired cardiovascular function or clinically significant cardiovascular diseases.
- Uncontrolled or symptomatic bone or regional metastases that are not stable or require steroids, are potentially life-threatening or have required radiation ≤ 28 days prior to starting study drug.
- Concomitant malignancies or previous malignancies with < 5-year disease-free interval at the time of randomization; patients with adequately resected basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or ductal carcinoma in situ may be enrolled irrespective of the time of diagnosis.
- Known positive serology for HIV, active hepatitis B and/or C.
- Prior randomization into this clinical study.

**Background**

- Serous carcinoma accounts for approximately 70% to 80% of epithelial ovarian cancers.1,2
- A 2-tier grading system reproducibly separates serous ovarian carcinoma into low-grade serous (LGS) or high-grade serous (HGS).3,4
- LGS carcinoma is far less common than HGS carcinoma and accounts for approximately 10% of all serous epithelial ovarian cancers.5
- LGS carcinoma is a unique tumor that is distinguished from HGS carcinoma not only by immunohistochemical profile, but also by molecular characteristics, epidemiologic features and clinical behavior.6
- Current therapies for LGS carcinomas (chemotherapy, hormonal) have demonstrated limited efficacy. Data from single-institution retrospective studies show an objective response rate (ORR) to both platinum- and non-platinum-based chemotherapies of ~4% and to hormonal therapies of ~8%.7,8
- Serous carcinomas of the ovary, fallopian tube and primary peritoneum have similar underlying pathologies and are often approached as a single disease entity with indistinguishable clinical courses.9
- KRAS or BRAF mutations, which activate the RAS/RAF/MEK/ERK signaling pathway, are present in many LGS carcinomas,10,11
- Aberrant signaling through the RAS/RAF/MEK/ERK pathway has been shown to lead to uncontrolled cell proliferation and cell transformation.12,13
- Binimetinib (MEK162) is an oral, potent, selective, allosteric, small-molecule inhibitor of MEK1/2, a key component of the RAS/RAF/MEK/ERK pathway, and has demonstrated activity in other disease settings where dysregulation of this pathway is present.14

**Study Design**

The MILO study is being conducted in collaboration with ENGOT (European Network of Gynaecological Oncological Trial groups).

**References**