A Phase 3, Randomized, Open-Label Study of Combination Therapy with Avutometinib plus Defactinib Versus Investigator's Choice of Treatment in Patients with Recurrent Low-Grade Serous Ovarian Cancer (LGSOC)

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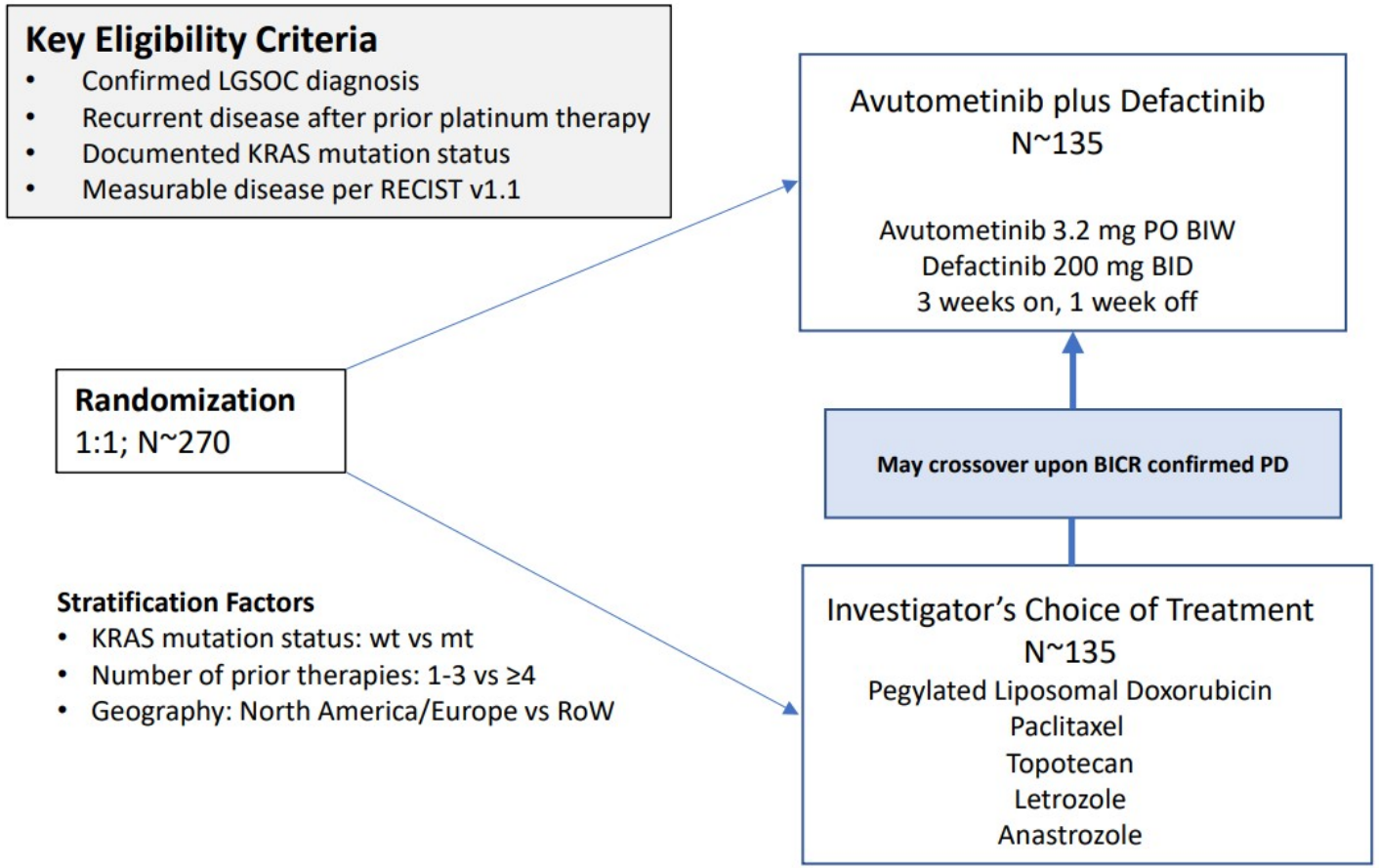

Primary Endpoint:
PFS via RECIST v1.1 per BICR

Secondary Endpoints*:
Overall Survival
PFS per RECIST v 1.1 per Investigator Assessment
Objective Response Rate
Duration of Response
Disease Control Rate
Safety
Pharmacokinetics
Patient Reported Outcomes

*Unless otherwise specified, all tumor response-based endpoint will be analyzed using both BICR and Investigator assessments.

Abbreviations: BICR = blinded independent central review; BID = twice a day; BIW = twice a week; KRAS-mt = KRAS-mutant tumor; KRAS-wt = KRAS-wild-type tumor; LGSOC = low-grade serous ovarian cancer; ORR = overall response rate; PD = progressive disease; PFS = progression free survival; RECIST = response evaluation criteria in solid tumors; RoW = Rest of World.

- 1. Age ≥ 18 years
- 2. Histologically **proven LGSOC (ovarian, fallopian, peritoneal)**
  - a. No mixed histology; LGSOC in conjunction with serous borderline tumor is permitted
  - b. Adequate tumor tissue (as defined in the lab manual) must be available for central confirmation of LGSOC. Adequate tumor tissue (as defined in the lab manual) must be received by the central laboratory prior to randomization. If the patient does not have adequate archived tumor tissue or the archived tumor was obtained more than 5 years from informed consent, then a fresh tumor sample will be needed to support eligibility. Central pathological confirmation does not need to be completed prior to randomization.
- 3. **Documented mutational status of KRAS** by an approved diagnostic test (eg, CDx, CE marked, etc) from tumor tissue Adequate tumor tissue and matched normal (as defined in the lab manual) must be received by the central laboratory prior to randomization. If the patient does not have adequate archived tumor tissue or the archived tumor was obtained more than 5 years from informed consent, then a fresh tumor sample will be needed to support eligibility. Central confirmation of mutational status does not need to be completed prior to randomization.
- 4. **Suitable for treatment with at least one of the Investigator's Choice of Treatments (ie, pegylated liposomal doxorubicin, paclitaxel, topotecan, letrozole, anastrozole)** as determined by the Investigator, given the medical history, prior treatment(s), availability, and approval within a given country, and other relevant factors.
- 5. Documented progression (radiographic or clinical) or recurrence of LGSOC after **at least one platinumbased chemotherapy regimen.** Allowed prior treatments and therapies include:
  - a. Prior systemic therapy for metastatic disease (International Federation of Gynecology and Obstetrics [FIGO] stage II-IV) may consist of chemotherapy administered with or without bevacizumab, with or without maintenance therapy; or hormonal therapy.
  - b. **One prior line of treatment with a MEK and/or RAF inhibitor is permitted only if there was prior clinical benefit (objective response or stable disease ≥ 6 months) and not received within 6 months of signing informed consent.**
- 6. At least one **measurable lesion according to RECIST v1.1**.
- 7. Eastern Cooperative Group (ECOG) performance status ≤ 1.
- 8. Adequate organ function, defined by the following laboratory parameters: a. Adequate hematologic function, including hemoglobin [Hb] ≥ 9.0 g/dL; platelets ≥100,000/mm3 ; and absolute neutrophil count [ANC] ≥ 1500/mm3 . If a red blood cell transfusion or erythropoiesisstimulating agent has been administered the Hb must remain stable and ≥ 9 g/dL for at least 1 week prior to first dose of study intervention.