TPS1129 **Poster Session**

ADELA: A double-blind, placebo-controlled, randomized phase 3 trial of elacestrant (ELA) + everolimus (EVE) versus ELA + placebo (PBO) in ER+/HER2- advanced breast cancer (aBC) patients with *ESR1*-mutated tumors progressing on endocrine therapy (ET) + CDK4/6i.

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Background: ET+CDK4/6i is standard-of-care (SOC) in 1L ER+/HER2- aBC; however, tumors eventually develop resistance. Constitutive activation in the PI3K/AKT/mTOR pathway can contribute to endocrine resistance in breast cancer. *ESR1* mutations are a common type of acquired resistance that emerges in 40-50% of patients in the metastatic setting after prolonged aromatase inhibitor exposure. There is an unmet need for novel therapeutic approaches to overcome resistance mechanisms and improve outcomes in patients with ER+/HER2- aBC with *ESR1*-mutated tumors progressing after ET+CDK4/6i. ELA is a next-generation oral SERD that binds to ER-alpha, inducing its degradation. In EMERALD, ELA improved PFS vs SOC ET in patients with *ESR1*-mutated tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) [Bidard 2022]. Differences were notable among patients who received prior ET+CDK4/6i ≥12 mo; median PFS with ELA was 8.6 mo vs 1.9 mo with SOC ET (HR 0.41; 95% CI 0.26-0.63) [Bardia 2024]. Crosstalk between ER and PI3K/AKT/mTOR pathways provides a rationale for evaluating ELA+EVE (a mTORC1 inhibitor). In ELEVATE phase 1b (NCT05563220), ELA+EVE demonstrated ORR 22% and CBR at 24 weeks 72% in patients with ER+/HER2- aBC progressing after ET+CDK4/6i; ELA 345 mg + EVE 7.5 mg was identified as the RP2D [Rugo ESMO 2024]. Safety was consistent with the known profile of EVE+SOC ET. ADELA compares ELA+EVE vs ELA+PBO in ER+/HER2- aBC patients with *ESR1*-mutated tumors progressing on ET+CDK4/6i. **Methods:** ADELA (NCT06382948) is an international, multicenter, double-blind, placebo-controlled phase 3 trial. Eligible patients are adults (≥18 yrs) with ER+/HER2- aBC and *ESR1*-mutated tumors, previously treated with 1-2 lines of ET for aBC, and evidence of disease progression on prior ET+CDK4/6i for aBC after ≥6 mo. Patients receiving CDK4/6i-based adjuvant therapy are eligible (disease progression must be confirmed after ≥12 mo of treatment but <12 mo following CDK4/6i completion). Other criteria include adequate organ function and ECOG PS 0-1. Exclusion criteria include prior chemotherapy for aBC and active uncontrolled/symptomatic brain metastasis. Patients will be randomized 1:1 to 28-d cycles of ELA 345 mg + EVE 7.5 mg QD or ELA 345 mg + PBO QD until disease progression or unacceptable toxicity. Patients will receive dexamethasone mouthwash during the first 8 wks. Stratification factors are presence of visceral metastases (yes vs no) and duration of prior CDK4/6i (≥12 mo vs <12 mo). The primary objective will be to evaluate PFS based on blinded independent review committee. Secondary endpoints include investigator-assessed PFS, OS, ORR, CBR, DoR, TTR, best percentage change in tumor burden, safety, and HRQoL. Status: Planned enrollment is 240 patients; recruitment is ongoing. Clinical trial information: NCT06382948. Research Sponsor: Menarini Group.