TPS1131 Poster Session

OPERA-01: A randomized, open-label, phase 3 study of palazestrant (OP-1250) monotherapy vs standard-of-care for ER+, HER2- advanced or metastatic breast cancer patients after endocrine therapy and CDK4/6 inhibitors.

Barbara Pistilli, Joohyuk Sohn, Peter Schmid, Meritxell Bellet, Lucia Del Mastro, Jane Lowe Meisel, Arlene Chan, Elisabeth de Kermadec, Lianqing Zheng, Heather L. McArthur; Breast Cancer Unit, Gustave Roussy, Villejuif, France; Yonsei University, Seoul, South Korea; Barts Cancer Institute, London, United Kingdom; Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; University of Genova; IRCCS Ospedale Policlinico San Martino, Genova, Italy; Winship Canter Institute of Emory University, Atlanta, GA; Breast Cancer Research Centre - WA & Curtin University, Nedlands, Australia; Olema Oncology, Cambridge, MA; Olema Oncology, San Francisco, CA; UT Southwestern Medical Center, Dallas, TX

Background: Endocrine therapy(ET) resistance is a major challenge in treating estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer (MBC); estrogen receptor (ESR1) mutations are an important mechanism of resistance. The standard of care (SOC) first-line treatment for ER+, HER2− MBC is ET plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Despite the benefit of ET and CDK4/6i, disease progression and acquired resistance to the combination remain a challenge. Novel, more effective ETs that can overcome resistance are needed to improve outcomes and delay time to chemotherapy. Palazestrant (OP-1250) is a novel oral, complete estrogen receptor antagonist (CERAN) and selective ER degrader (SERD) that acts by blocking both transcriptional activation function domains, AF1 and AF2, regardless of ESR1 mutation status. As monotherapy, palazestrant showed a tolerable safety profile, favorable pharmacokinetics and encouraging antitumor efficacy in heavily-pretreated patients during phase 1/2 studies, regardless of *ESR1* mutation status (NCT04505826; Lin et al. ESMO 2023 MO382). **Methods:** OPERA-01 (NCT06016738) is a multicenter, randomized, open-label, phase 3 clinical trial comparing the efficacy and safety of palazestrant as a single agent to SOC ET (fulvestrant, anastrozole, letrozole, or exemestane) in patients with ER+, HER2− MBC that relapsed or progressed on 1-2 prior lines of ET, including a CDK4/6i. Adult patients are eligible with a diagnosis of evaluable ER+, HER2− inoperable locally advanced or MBC and an Eastern Cooperative Oncology Group performance status of 0 or 1. Prior treatments must include 1 or 2 prior lines of ET with the last ET duration of ≥6 months; must have received and have disease progression on CDK4/6i with ET for MBC. Prior chemotherapy for MBC is not allowed. The study included a dose selection phase, where participants were randomized to 90 mg qd or 120 mg qd palazestrant or SOC; enrollment in this phase is complete. After the dose selection of palazestrant, the study will continue with the selected dose compared to SOC ET at a 1:1 randomization. Overall, 510 patients will be randomized to palazestrant or SOC ET during the study. The primary endpoint of progression-free survival will be assessed by blinded independent central review in patients with and without *ESR1* mutations (dual primary endpoint). Secondary endpoints include overall survival, antitumor activity (objective response rate, clinical benefit rate, and duration of response), safety, exposure and patient-reported outcomes in patients with and without *ESR1* mutations. Study recruitment began in November 2023. Clinical trial information: NCT06016738. Research Sponsor: Olema Oncology.