

PRESENTATION: ORAL PRESENTATION (GENERAL SESSION)

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1197 – OPERA-02: a phase 3, randomized, double-blind, active-controlled study of palazestrant with ribociclib versus letrozole with ribociclib for the first-line treatment of ER+, HER2– advanced breast cancer

Gustavo Werutsky¹, Barbara Pistilli¹, Virginia F Borges¹, Wolfgang Anni¹, Komal L. Jhaveri¹, Peter Schmid¹, Kenneth Caldwell¹, Sara M. Tolaney¹

¹Latin American Cooperative Oncology Group (LACOG) – Porto Alegre (RS), Brazil.

Estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) disease accounts for 70% of advanced breast cancer (ABC). The standard first-line treatment is an aromatase inhibitor (AI) plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Ribociclib is the only CDK4/6i that, when combined with Ais, improved both progression-free survival (PFS) and overall survival (OS) in ER+, HER2– ABC. Despite this, endocrine resistance develops in many patients, often due to AI-induced activating mutations in the ESR1 gene. Early sustained suppression of both wild-type and mutated ERs during first-line treatment of ER+, HER2– ABC may enhance endocrine sensitivity, delay resistance to endocrine therapy, and improve clinical outcomes. Palazestrant (OP-1250) is a novel oral, complete estrogen receptor antagonist and selective estrogen receptor degrader (SERD). Early palazestrant studies showed favorable safety and encouraging antitumor activity both as monotherapy and in combination with ribociclib, regardless of ESR1 mutation status. Palazestrant showed no clinically meaningful drug interactions with ribociclib, and the combination safety profile was consistent with the known profiles of each drug. OPERA-02 (NCT07085767) is a phase 3, international, multicenter, randomized, double-blind study evaluating the efficacy and safety of palazestrant plus ribociclib *versus* letrozole plus ribociclib as first-line treatment for ER+, HER2– ABC. Approximately 1,000 patients will be randomized 1:1 to palazestrant plus ribociclib or letrozole plus ribociclib, with matching placebos. The primary endpoint is investigator-assessed PFS; secondary endpoints are OS, PFS by blinded independent review committee, overall response rate, duration of response, clinical benefit rate, safety, pharmacokinetics, patient-reported outcomes, and PFS2. Adults with de novo or recurrent endocrine therapy-sensitive disease and no prior systemic therapy for ABC are eligible. Patients must have measurable disease or evaluable bone disease, ECOG 0–1, and adequate organ function. Those with contraindication to ribociclib were excluded. Pre- or perimenopausal women and men must receive gonadotropin-releasing hormone agonists. The study is recruiting globally.

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