

Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

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Abstract

Background: Endocrine therapy-based neoadjuvant treatment for luminal breast cancer allows efficient testing of new combinations before surgery. The activation of the phosphatidylinositol-3-kinase (PI3K) pathway is a known mechanism of resistance to endocrine therapy. Taselisib is an oral, selective PI3K inhibitor with enhanced activity against PIK3CA-mutant cancer cells. The LORELEI trial tested whether taselisib in combination with letrozole would result in an increased proportion of objective responses and pathological complete responses.

Methods: In this multicentre, randomised, double-blind, parallel-cohort, placebo-controlled phase 2, study, we enrolled postmenopausal women (aged ≥18 years) with histologically confirmed, oestrogen receptor (ER)-positive, HER2-negative, stage I-III, operable breast cancer, from 85 hospitals in 22 countries worldwide. To be eligible, patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status 0-1, adequate organ function, and had to have evaluable tumour tissue for PIK3CA genotyping. Patients were randomly assigned (1:1) by means of a permuted block algorithm (block size of four) via an interactive voice or web-based response system, to receive letrozole (2.5 mg/day orally, continuously) with either 4 mg of oral taselisib or placebo (on a 5 days-on, 2 days-off schedule) for 16 weeks, followed by surgery. Randomisation was stratified by tumour size and nodal status. Site staff, patients, and the sponsor were masked to treatment assignment. Coprimary endpoints were the proportion of patients who achieved an objective response by centrally assessed breast MRI and a locally assessed pathological complete response in the breast and axilla