Neoadjuvant letrozole in postmenopausal estrogen and/or progesterone receptor positive breast cancer: a phase IIb/III trial to investigate optimal duration of preoperative endocrine therapy.

BACKGROUND: In recent years, preoperative volume reduction of locally advanced breast cancers, resulting in higher rates of breast-conserving surgery (BCS), has become increasingly important also in postmenopausal women. Clinical interest has come to center on the third-generation nonsteroidal aromatase inhibitors (AIs), including letrozole, for such neoadjuvant endocrine treatment. This usually lasts 3-4 months and has been extended to up to 12 months, but optimal treatment duration has not been fully established. METHODS: This study was designed as a multicenter, open-label, single-arm, exploratory phase IIb/III clinical trial of letrozole 2.5 mg, one tablet daily, for 4-8 months. The primary objective was to investigate the effect of neoadjuvant treatment duration on tumor regression and BCS eligibility to identify optimal treatment duration. Tumor regression (by clinical examination, mammography, and ultrasound), shift towards BCS eligibility, and safety assessments were the main outcome measures. Standard parametric and nonparametric descriptive statistics were performed. RESULTS: Letrozole treatment was received by 32 of the enrolled 33 postmenopausal women (median (range): 67.0 (56-85) years)
with unilateral, initially BCS-ineligible primary breast cancer (clinical stage \( T2, N0, M0 \)). Letrozole treatment duration in the modified intent-to-treat (ITT; required 4 months’ letrozole treatment) analysis population (29 patients) was 4 months in 14 patients and > 4 months in 15 patients. The respective per-protocol (PP) subgroup sizes were 14 and 11. The majority of partial or complete responses were observed at 4 months, though some beneficial responses occurred during prolonged letrozole treatment. Compared with baseline, median tumor size in the ITT population was reduced by 62.5% at Month 4 and by 70.0% at final study visit (Individual End). Similarly, in the PP population, respective reductions were 64.0% and 67.0%. Whereas initially all patients were mastectomy candidates, letrozole treatment enabled BCS (lumpectomy) in 22 ITT (75.9%) and 18 PP (72.0%) patients. CONCLUSION: Over half of patients become BCS-eligible within 4 months of preoperative letrozole treatment. While prolonged treatment for up to 8 months can result in further tumor volume reduction in some patients, there is no clear optimum for treatment duration. Letrozole has a favorable overall safety and tolerability profile. TRIAL REGISTRATION: ClinicalTrials.gov identifier NCT00535418.