Association of Somatic Driver Alterations With Prognosis in Postmenopausal, Hormone Receptor-Positive, HER2-Negative Early Breast Cancer: A Secondary Analysis of the BIG 1-98 Randomized Clinical Trial

Stephen J Luen, Rebecca Asher, Chee Khoon Lee, Peter Savas, Roswitha Kammler, Patrizia Dell'orto, Olivia Maria Biasi, David Demanse, Lellean JeBailey, Sinead Dolan, Wolfgang Hackl, Beat Thürlimann, Giuseppe Viale, Marco Colleoni, Meredith M Regan & Sherene Loi

Importance
A range of somatic driver alterations has been described in estrogen receptor-positive, HER2-negative (ER+/HER2-) early breast cancer (BC); however, the clinical relevance is unknown.

Objective
To investigate associations of driver alterations with prognosis and the role of PIK3CA mutations in prediction of benefit associated with endocrine therapy in postmenopausal patients with ER+/HER2- early BC treated with tamoxifen or letrozole.

Design, Setting, and Participants
The Breast International Group (BIG) 1-98 trial randomized 8010 postmenopausal patients with hormone receptor-positive, operable, invasive BC to monotherapy with letrozole, tamoxifen, or a sequential strategy for 5 years. Driver alterations were characterized using next-generation sequencing in primary tumors from a subset of 764 patients from 7329 eligible patients with ER+/HER2- BC, with 841 distant recurrences after a median of 8.1 years of follow-up. To correct for the oversampling of distant recurrences, weighted analysis methods were used. This analysis was conducted from April 4, 2016, to November 30, 2016.

Main Outcomes and Measures
The prevalence of driver alterations, associations with clinicopathologic factors, distant recurrence-free interval, and treatment interactions were analyzed. Multivariable analyses were performed to adjust for clinicopathologic factors.

Results
Of 764 samples, 538 (70.4%), including 140 distant recurrence events, were successfully sequenced. Nineteen driver alterations were observed with 5% or greater frequency, with a mean of 4 alterations (range, 0-15) per tumor. PIK3CA mutations were the most common (49%) and were significantly associated with reduction in the risk for distant recurrence (hazard ratio [HR], 0.57; 95% CI, 0.38-0.85; P = .006). TP53 mutations (HR, 1.92; 95% CI, 1.21-3.04; P = .006), amplifications on 11q13 (HR, 2.14; 95% CI, 1.36-3.37; P = .001) and 8p11 (HR, 3.02; 95% CI, 1.88-4.84; P < .001), and increasing number of driver alterations (HR per additional alteration, 1.18; 95% CI, 1.11-1.25; P < .001) were associated with significantly greater risk. Amplifications on 11q13 and 8p11 remained significant predictors in multivariable analysis, but not PIK3CA and TP53 mutations. Patients with tumors harboring kinase or helical domain PIK3CA mutations derived significantly greater benefit from letrozole over tamoxifen than patients whose tumors did not (P interaction = .002).

Conclusions and Relevance
In ER+/HER2- postmenopausal, early-stage BC, amplifications on 11q13 and 8p11 were significantly associated with increased risk for distant recurrence and PIK3CA mutations were predictive of greater magnitude of benefit from letrozole. With these findings, DNA-based classification may aid adjuvant treatment decision making in this setting.

Trial Registration
ClinicalTrials.gov Identifier: NCT00004205.