

Evaluation of everolimus (EVE) in HER2+ advanced breast cancer (BC) with activated PI3K/mTOR pathway: exploratory biomarker observations from the BOLERO-3 trial

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Background: In BOLERO-3 (NCT01007942; Novartis), a randomized, double-blind, placebo-controlled, phase 3 trial (N=569), EVE 5 mg daily combined with weekly trastuzumab and vinorelbine significantly prolonged progression-free survival (PFS) vs placebo in patients with trastuzumab-resistant HER2+ advanced BC previously treated with a taxane (HR=0.78, 95% CI: 0.65-0.95). Correlations between key members of the PI3K/mTOR pathway and EVE efficacy were explored in a subset of patients for the identification of potential predictive biomarkers.

Materials and Methods: pS6 and PTEN levels were assessed in archival tumor samples by IHC and PIK3Ca gene mutations in exons 9 and 20 were identified by DNA sequencing. Correlations between the biomarker data and PFS were evaluated by univariate and multivariate Cox models.

Results: Of 283 available patients, 262 had evaluable data for one or more of the measured biomarkers. This biomarker population was representative of the trial population in terms of demographics, clinical characteristics, and efficacy outcomes. None of the known prognostic factors were significantly imbalanced between the arms. Patients with low PTEN level (optimal H-score cut-point: <20th percentile) derived more benefit with EVE (HR=0.40, 95% CI: 0.2-0.82) with a median PFS gain of 4.4 months (EVE 9.6 months vs placebo 5.2 months). Similarly, patients with high pS6 level (optimal H-score cut-point: >75th percentile) derived more benefit with EVE (HR=0.48, 95% CI: 0.24-0.96). In contrast, patients with low pS6 or normal PTEN did not appear to derive any benefit from addition of EVE (HR=1.14, 95% CI: 0.77-1.68 and HR=1.05, 95% CI: 0.75-1.45, respectively). A trend of enhanced EVE treatment benefit was observed in patients with PIK3Ca mutations (~20% of the population) and in those with activated PI3K pathway, defined as harboring either PIK3Ca mutation or low PTEN level. Significant treatment-marker interaction was detected for PTEN and pS6 ($P=0.01$ and 0.04 , respectively), but not for PIK3Ca ($P=0.32$).

Conclusions: Patients in BOLERO-3 with biomarkers indicative of PI3K/mTOR pathway activation may derive greater benefit from addition of EVE to trastuzumab and vinorelbine. These observations are consistent with the hypothesis that mTOR inhibition attenuates trastuzumab resistance resulting from PI3K/mTOR pathway activation. The results and clinical implications of this exploratory analysis need further validation and investigation.