No Survival Benefit When Adding Everolimus to Trastuzumab and Paclitaxel in Advanced HER2-Positive BC

Written by Nicola Parry

Sara A. Hurvitz, MD, University of California at Los Angeles, Los Angeles, California, USA, shared data from the Everolimus in Combination With Trastuzumab and Paclitaxel in the Treatment of HER2 Positive Locally Advanced or Metastatic Breast Cancer trial [BOLERO-1; NCT00876395]. The data showed that adding everolimus to combination trastuzumab and paclitaxel therapy did not improve progression-free survival (PFS) in women with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (BC).

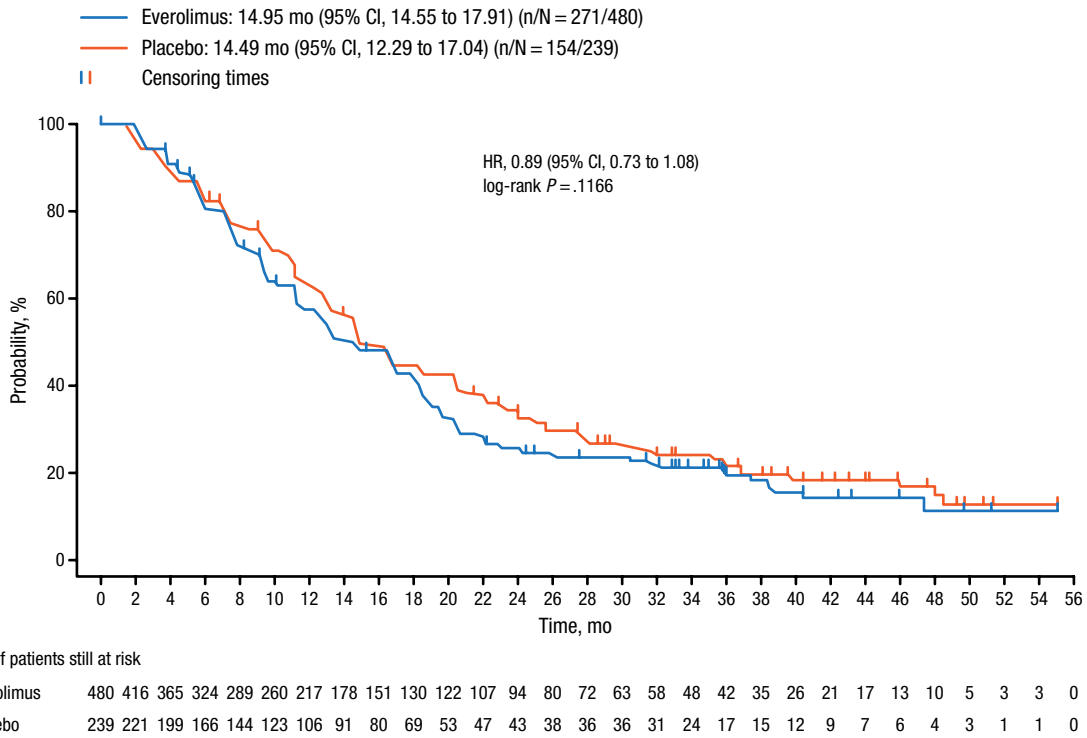
Resistance to trastuzumab remains a significant challenge in the treatment of HER2-positive BC, said Dr Hurvitz, adding that hyperactivation of the phosphoinositide-3 kinase/mammalian target of rapamycin (mTOR) pathway has been implicated in this resistance [Hurvitz SA et al. *Cancer Treat Rev.* 2013], and mTOR inhibitors have shown some potential to increase PFS in this patient population [André F et al. *Lancet Oncol.* 2014].

The phase 3 BOLERO-1 trial was subsequently conducted in patients (n = 719) with locally advanced or metastatic HER2-positive BC who had received no prior therapy (other than endocrine therapy, prior adjuvant or neoadjuvant trastuzumab therapy, or chemotherapy). Participants were randomized 2:1 to receive everolimus (10 mg PO daily) plus weekly paclitaxel and trastuzumab, or placebo plus weekly paclitaxel and trastuzumab. Treatment continued to the point of disease progression or intolerable toxicity.

The primary end point was PFS in the entire study population and in a hormone receptor–negative subgroup of patients. Secondary end points included overall response rate (ORR), clinical benefit rate (CBR), and safety.

At the time of the final analysis, performed after 425 PFS events in the entire study population, there was no significant difference in median PFS between the everolimus and placebo arms (14.95 vs 14.49 months; HR, 0.89; 95% CI, 0.73 to 1.08; log-rank $P = .1166$; Figure 1).

Figure 1. Progression-Free Survival in the BOLERO-1 Entire Study Population



One-sided *P* value is obtained from the log-rank test stratified by prior use of trastuzumab (yes/no) and visceral metastasis (yes/no) from Interactive Web Response System.
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PFS was increased with everolimus therapy in the hormone receptor-negative subgroup (20.27 vs 13.08 months; HR, 0.66; log-rank $P = .0049$); however, this did not cross the statistical significance threshold of $P = .0044$ as prespecified in the study protocol, and was therefore considered statistically insignificant.

Similarly, there was no significant difference in the secondary end points of ORR ($P = .7276$ vs $P = .4085$) and CBR ($P = .9573$ vs $P = .6382$) in the entire study population or the hormone receptor-negative subgroup, respectively.

Dr Hurvitz reported increased rates of any-grade stomatitis (67% vs 32%), diarrhea (57% vs 47%), neutropenia (38% vs 25%), and anemia (31% vs 16%) in patients who received everolimus compared with the placebo group. Additionally, on-treatment deaths due to an adverse event (AE) occurred in 3.6% of patients in the everolimus arm, compared with 0 in the placebo arm. All except 1 of these deaths occurred within 15 months of the beginning of the study, she said, adding that this may be associated with a lack of experience in managing the AEs of everolimus in combination with chemotherapy. Careful monitoring and early management of AEs in patients who receive everolimus and chemotherapy is therefore important, she concluded.

Results From the EPO-ANE-3010 Study Consistent With US Black Box Labeling

Written by Muriel Cunningham

Safety concerns regarding erythropoiesis-stimulating agents led to a 2004 US Food and Drug Administration request for a postmarketing study to determine the effect of epoetin alfa (EPO) on progression-free survival (PFS) in patients with metastatic breast cancer (MBC). As a result of this request, the phase 3, randomized, multicenter, open-label, noninferiority EPO-ANE-3010 study [NCT00338286] was conducted to rule out a hazard ratio (EPO vs control) of ≥ 1.15 for PFS in patients with MBC. Brian Leyland-Jones, MD, Avera Cancer Institute, Sioux Falls, South Dakota, USA, presented the design and results of this study.

Key inclusion criteria were a hemoglobin value ≤ 11 g/dL, receiving first- or second-line chemotherapy, at least 2 cycles planned, Eastern Cooperative Oncology Group performance status of 0 or 1, and at least 1 measurable metastatic lesion at the start of chemotherapy. Patients were excluded if they met any of the following criteria: bone-only metastases, brain metastases or central nervous system involvement, anemia due to other causes, taking endocrine or anticoagulant therapy, a thrombotic vascular event (TVE) within the previous 12 months, or an arterial thrombosis within 6 months. Eligible patients were randomized 1:1 to either standard chemotherapy plus standard of care (SOC) or standard chemotherapy plus EPO 40 000 IU weekly plus SOC. The primary end point was PFS, and overall survival (OS), time to tumor progression (TTP), and TVE incidence and severity were secondary end points. The protocol was amended mid-study to have the investigators determine progressive disease (PD) instead of the independent review committee (IRC).

A total of 2098 subjects were included in the intent-to-treat data set (1050 in the EPO group and 1048 in the SOC group). The majority of patients (84%) were enrolled in Ukraine, India, Georgia, and Russia. The treatment groups were well balanced. The median age was 52 years (range, 23 to 81 years), 80% were receiving first-line chemotherapy, 39% were HER2-positive, and 88% had visceral disease. The median number of EPO doses was 8.0 (range, 1 to 70), with a median weekly dose of 32 316.7 IU (range, 2269 to 53 721). Of note was that mean hemoglobin values were similar between the 2 treatment groups, with the separation being consistently < 1 g/dL throughout the study.

The primary end point of PFS based on investigator-determined PD did not meet the protocol-specified criteria for noninferiority. Results using IRC-determined PD were similar. All subgroup analyses of the primary end point favored the SOC group. Grade 3 adverse events were similar between the 2 groups. The EPO group had 29 (2.8%) confirmed TVEs, compared with 15 (1.4%) in the SOC group.

In his concluding remarks, Dr Leyland-Jones noted that while the researchers had hoped for better results, the findings from this study are consistent with the current US black box labeling for EPO.