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.