

## Balance of efficacy and toxicity varies with trastuzumab for early breast cancer

**U**pdated results of the BCIRG (Breast Cancer International Research Group) 006 trial show that integrating trastuzumab (Herceptin) into docetaxel (Taxotere)-containing adjuvant chemotherapy improves disease-free survival for women with early-stage breast cancer positive for HER2/*neu*. However, the efficacy-toxicity profile varies with the regimen used, according to Dennis J. Slamon, MD, PhD, chief of the division of hematology-oncology at the University of California, Los Angeles, who presented the results of this phase III trial's second interim analysis.

A total of 3,222 women who had early-stage, node-positive or high-risk node-negative breast cancer that overexpressed HER2/*neu* were randomized to three treatment groups:

- Doxorubicin and cyclophosphamide followed by docetaxel (AC→T) (control);
- Doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH);
- Docetaxel, carboplatin, and trastuzumab (TCH).

"[This] was the only one of the Herceptin trials in which a nonanthracycline-based arm was included," Dr. Slamon noted. As of this second interim analysis, the median follow-up was 3 years.

Four years after randomization, estimated disease-free survival was 83% in the AC→TH arm and 82% in the TCH arm, compared with 77% in the AC→T (control) arm. The corresponding hazard ratios, both significant, were 0.61 and 0.67. Viewed another way, the absolute disease-free survival benefit between years 2 and 4 was 5%–6% with trastuzumab. Overall survival was also significantly

better for the AC→TH (0.59) and TCH (0.66) groups.

In analyses restricted to the 29% of patients who had node-negative disease, the benefit was even greater. Disease-free survival events were significantly reduced by more than half with AC→TH (hazard ratio, 0.32) and with TCH (0.47) compared with AC→T. Furthermore, the risk of death was significantly lower with AC→TH (0.16) and nonsignificantly so with TCH (0.42).

### 'Noteworthy safety issues with AC→TH'

When compared with the AC→T (control) regimen, the TCH regimen was associated with significantly lower rates of neuropathy and myalgia of any grade as well as of grade 3/4 arthralgia, myalgia, hand-foot syndrome, stomatitis, and vomiting. Also, the TCH regimen had a significantly lower rate of grade 3/4 leukopenia but a significantly higher rate of grade 3/4 neutropenia. Both grade 3/4 anemia and thrombocytopenia were significantly more common with AC→TH than with AC→T.

"There are now four leukemias in the anthracycline-containing arms," Dr. Slamon pointed out (three with AC→T and one with AC→TH). "We have not yet seen any in the TCH arm."

"In my biased opinion, the only toxicity that Herceptin has ever had has been...cardiotoxicity," Dr. Slamon commented, particularly when used with an anthracycline, as in this instance. The number of patients who developed grade 3/4 cardiac toxicity was significantly higher in the AC→TH arm—but not in the TCH arm—relative to the AC→

T (control) arm. Similarly, the proportion of patients with a more than 10% reduction in left ventricular ejection fraction (LVEF) was significantly higher in the AC→TH arm (18%)—but not in the TCH arm (9%)—compared with the AC→T arm (10%).

"Cardiac toxicity has held true," Dr. Slamon added, and the question is how long lasting is it? Many investigators have argued that it "goes away," he noted. However, with follow-up out to 900 days from randomization, the depression of LVEF seen in the AC→TH group has persisted. "It appears to be sustained at some level for a long period."

In a subset of 2,990 patients, topoisomerase II amplification—a predictor of response to anthracyclines—was present along with HER2/*neu* amplification in 35%. Treatment effects differed by coamplification status. In patients with topoisomerase II coamplification, neither AC→TH nor TCH yielded better disease-free survival than AC→T. "You buy more toxicity with the AC→T arm and certainly more with the AC→TH arm," Dr. Slamon said. In contrast, in patients without topoisomerase II coamplification, both AC→TH and TCH yielded significantly better disease-free survival than AC→T.

Slamon D, Eiermann W, Robert N, et al. BCIRG 006: 2<sup>nd</sup> interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin, and trastuzumab (TCH) in Her2/*neu* positive early breast cancer patients. Paper presented at the 29<sup>th</sup> Annual Meeting of the San Antonio Breast Cancer Symposium; December 14–17, 2006; San Antonio, Tex. Abstract 52.