This Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of docetaxel plus prednisone as first-line treatment for CRPC. Chemotherapy-naïve patients with progressive metastatic CRPC (effective castration defined as serum testosterone levels <50 ng/dL) and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score ≥2 were randomized to either lenalidomide (25 mg on Days 1 to 14) plus docetaxel (75 mg/m$^2$ on Day 1 of each cycle) plus prednisone (5 mg BID on Days 1 to 21) or placebo plus docetaxel plus prednisone at similar doses and scheduling. Treatment phase was 21-day cycles until disease progression. Follow-up for survival occurred every 90 days for up to 5 years following study treatment discontinuation. The primary study endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response, and safety. Patient enrollment was completed in November 2011, with a total of 1059 patients. The data analysis results were based on the cutoff date of January 13, 2012.

The lenalidomide (n=533) and placebo (n=526) arms were well balanced; mean age was 69 years, and ECOG PS scores were 0 in 48.1% and ≥1 in 51.8% of patients. About 71% of patients had radiographic disease progression. Metastatic sites included bone, soft tissue, and both bone and soft tissue. Median OS and PFS were 77 and 45 weeks in the lenalidomide arm, compared with median not reached (HR, 1.53; 95% CI, 1.17 to 2.00; p=0.0017) and 46 weeks (HR, 1.32; 95% CI, 1.05 to 1.66; p=0.0187; in the placebo arm, respectively. Objective response rate was 22.1 % for lenalidomide versus 24.3% for the placebo arm (p=0.3975). The median number of cycles administered were 6 and 8 in the lenalidomide and placebo arms, respectively. All dose reductions were due to adverse events, except for 2 dose reductions of docetaxel that were due to other reasons.

The most common grade ≥3 adverse events that occurred significantly more often in the lenalidomide group included neutropenia (22%), febrile neutropenia (12%), diarrhea (7%), and pulmonary embolism (6.5%). Significantly more deaths (>28 days from last lenalidomide dose) occurred in the lenalidomide arm (20.8%) compared with the placebo arm (15.0%; p=0.016).

The addition of lenalidomide to docetaxel plus prednisone did not improve OS in patients with CRPC and was associated with greater toxicity. Shorter treatment duration, earlier treatment discontinuation, and lower dose intensity of docetaxel might have contributed to this lack of benefit. Studies to explain the poorer outcome of the lenalidomide arm are under way.

## Two Years Versus One Year of Trastuzumab in Patients with Early Breast Cancer

*Written by* ***Tony Rizzo***

The 2005 results of large randomized trials, including the Trastuzumab in Treating Women with Primary Breast Cancer [HERA; NCT00045032] trial, demonstrated statistically significant disease-free survival (DFS) benefit for 1 year of treatment with trastuzumab compared with observation in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. After 2005, the HERA trial focused on the secondary objective of comparing 2 years of trastuzumab treatment with 1 year of treatment. The results of this analysis were presented by Richard D. Gelber, MD, PhD, International Breast Cancer Study Group Statistical Center, Boston, Massachusetts, USA.

A total of 5102 patients with HER2-positive invasive early breast cancer were randomized after adjuvant treatment to observation (1698), 1 year of trastuzumab (n=1703), or 2 years of trastuzumab (n=1701). Patients in the observation group had the option to switch to trastuzumab in 2005. Patients included in the 2 years (n=1553) versus 1 year (n=1552) of trastuzumab analysis were those who remained disease-free for at least 366 days from randomization. For the safety analysis, primary cardiac events were defined as NYHA Class III/IV plus left ventricular ejection fraction (LVEF) <50% and ≥10% below baseline, or cardiac death. Secondary cardiac events were defined as LVEF <50% and ≥10% below baseline, excluding patients with a primary cardiac event.

At 8 years of median follow-up, DFS rates were 75.8% in the 2-year group versus 76.0% in the 1-year group (HR, 0.99; 95% CI, 0.85 to 1.14; p=0.86). DFS was not significantly different with 2 years versus 1 year of trastuzumab in either hormone receptor-positive (76.1% vs 77.2%; HR, 1.05; 95% CI, 0.85 to 1.29; p=0.67) or -negative (75.4% vs 74.7%; HR, 0.93; 95% CI, 0.76 to 1.14; p=0.51) patients. OS rates at 8 years of median follow-up were 86.4% with 2 years of treatment versus 87.6% with 1 year of treatment (HR, 1.05; 95% CI, 0.86 to 1.28; p=0.63).

In the safety analysis population, grade 3/4 adverse events (AEs) were reported in 20.4% of the 2-year group (n=1673), 16.3% of the 1-year group (n=1682), and 8.2% of the observation group (n=1744). Fatal AEs occurred in 1.2% of the 2-year group, 1.1% of the 1-year group, and 0.4% of the observation group. Primary cardiac events occurred in 1.0% of the 2-year group, 0.8% of the 1-year group, and

0.1% of the observation group. Secondary cardiac events occurred in 7.2% of the 2-year group, 4.1% of the 1-year group, and 0.9% of the observation group.

Results at median follow-up of 8 years also demonstrated sustained and statistically significant DFS and OS benefits with 1 year of trastuzumab treatment versus observation in the intention-to-treat analysis despite selective crossover.

The authors concluded that 2 years of treatment with trastuzumab did not provide long-term benefit compared with 1 year of treatment when administered as sequential treatment following chemotherapy. Cardiac toxicity and other AEs were increased in the 2-year treatment arm. The HERA results confirm that 1 year of trastuzumab treatment is the standard of care as part of adjuvant therapy for patients with HER2-positive early breast cancer.

## Adjuvant Trastuzumab for 6 Versus 12 Months in Patients with Early Breast Cancer

*Written by* ***Toni Rizzo***

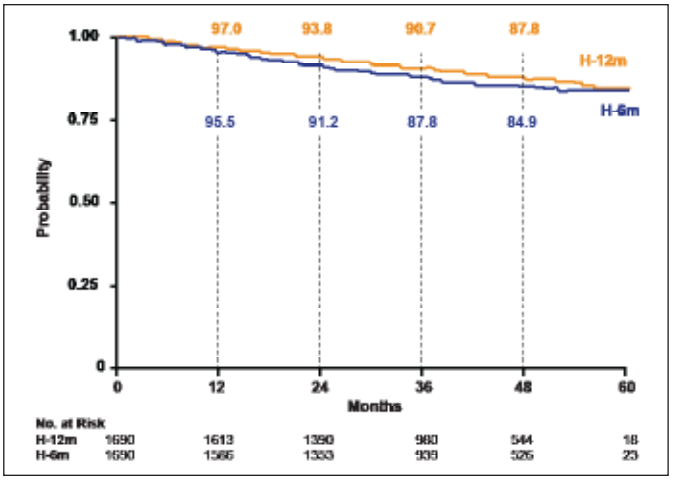
One year of adjuvant treatment with trastuzumab improves survival in patients with human epidermal growth factor 2 (HER2)-positive early breast cancer [Piccart-Gebhart MJ et al. *N Engl J Med* 2005; Romond EH et al. *N Engl J Med* 2005]. The Finland Herceptin [FinHer] trial showed that patients treated with 9 weeks of adjuvant trastuzumab also had a similar survival benefit [Joensuu H et al. *N Engl J Med* 2006]. The FinHer results and concerns about cardiac toxicity with trastuzumab provided the rationale for the Trastuzumab for 6 Months or 1 Year in Treating Women with Nonmetastatic Breast Cancer That Can Be Removed by Surgery [PHARE; NCT00381901] trial presented by Xavier Pivot, MD, Institut National du Cancer, Boulogne-Billancourt, France. The primary objective of this noninferiority trial was to compare the effect of 6 versus 12 months of adjuvant treatment with trastuzumab on disease-free survival (DFS) in patients with HER2-positive early breast cancer.

A total of 3384 patients undergoing treatment with trastuzumab were randomized to continue treatment for 12 months (n=1690) or to stop treatment at 6 months (n=1690). The patients were stratified according to estrogen receptor status, and concurrent or sequential chemotherapy. Patients were evaluated with a clinical exam and left ventricular ejection fraction (LVEF) every 3 months for up to 24 months, and at 30 months. Mammography was performed every 6 months for up to 60 months. The primary endpoint was DFS; secondary endpoints were overall survival (OS) and cardiac toxicity.

Baseline patient characteristics were well balanced between the 2 study groups. About 58% of patients in both groups received concomitant chemotherapy, while about 42% received sequential chemotherapy. The mean duration of trastuzumab therapy was 11.8 months in the 12-month group and 6.3 months in the 6-month group.

At median follow-up of 42.5 months, DFS events occurred in 10.4% (176 events) of patients treated for 12 months versus 13.0% (219 events) of those treated for 6 months (HR, 1.28; 95% CI, 1.05 to 1.56; p=0.29; Figure 1). The DFS events in the 12-month versus the 6-month treatment group included local recurrence (1.1% vs 1.4%), regional recurrence (0.6% vs 0.5%), and distant recurrence (6.4% vs 8.3%). Contralateral breast cancer occurred in 0.4% of the 12-month treatment group and 0.7% of the 6-month treatment group, and a second primary malignancy was reported in 1.5% of patients in each group. There were 66 deaths in the 12-month group versus 93 deaths in the 6-month group (HR, 1.47; 95% CI, 1.07 to 2.02; no p value reported).

**Figure 1. Disease-Free Survival.**

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The cardiac event (composite of clinical and LVEF findings) rate was 5.7% in the 12-month group versus 1.9% in the 6-month group (p<0.0001). LVEF was <50% in 6.3% of the 12-month group versus 4.7% in the 6-month group (p=0.04); it was <50% and decreased by >10% in 4.8% of the 12-month group versus 3.6% of the 6-month group (p=0.071); it was >50% and decreased by >15% in 7.4% of the 12-month group versus 7.0% of the 6-month group (not significant).