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***

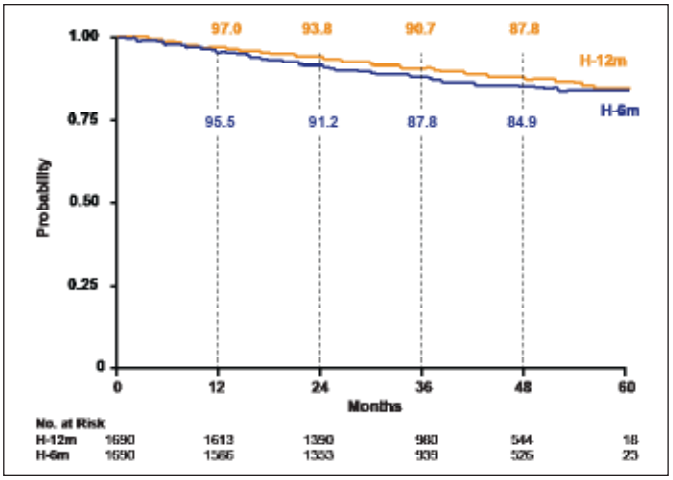
One year of adjuvant treatment with trastuzumab improves survival in patients with human epidermal growth factor 2 (HER2)-positive early breast cancer [Piccart-Gebhart MJ et al. *N Engl J Med* 2005; Romond EH et al. *N Engl J Med* 2005]. The Finland Herceptin [FinHer] trial showed that patients treated 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).

The results of the PHARE trial were inconclusive for the noninferiority hypothesis. Nevertheless, a trend favoring the standard 12 months of treatment in DFS and OS was observed.

Breast Cancer: Updated Overall Survival Results from EMILIA

Written by ***Phil Vinall***

Trastuzumab emtansine (T-DM1) is a human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate, composed of trastuzumab, a stable thioether linker, and the potent cytotoxic, microtubule inhibitor DM1. It retains the HER2-directed antitumor properties of trastuzumab and allows for the intracellular delivery of T-DM1 [LoRusso PM et al. *Clin Cancer Res* 2011]. Preclinical studies have shown T-DM1 to be up to 500 times more potent than taxane. Sunil Verma, MD, Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada, reported updated study results of a trial showing that progression-free survival (PFS) and overall survival (OS) significantly improved in patients with breast cancer treated with T-DM1 compared with capecitabine (CAP) plus lapatinib (LAP). The study was published to coincide with the presentation [Verma S et al. *N Engl J Med* 2012].

An Open-Label Study of Trastuzumab Emtansine versus Capecitabine+Lapatinib in Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer [EMILIA; NCT00829166] was a randomized Phase 3 trial evaluating T-DM1 compared with CAP plus LAP. Patients with HER2-positive locally advanced or metastatic breast cancer, previously treated with taxane and trastuzumab were randomized to intravenous T-DM1 (3.6 mg/kg every 3 weeks; n=495) or oral CAP (1000 mg/m^2 BID on Days 1 to 14 every 3 weeks plus oral LAP 1250 mg QD on Days 1 to 21; n=496). The primary study end points were PFS, OS, and safety.

Subjects were a median age of 53 years, mostly White, and had an Eastern Cooperative Oncology Group Performance Status score of 0 (61% to 64%) or 1 (36% to 39%). Up to 80% of patients had measurable disease; up to 68% had visceral disease, and up to 33% had at least 3 sites of metastatic disease. About 55% of patients were estrogen and/or progesterone (ER/PR)-positive.

The final PFS and first interim OS analyses were presented at the 2012 annual American Society of Clinical Oncology meeting [Blackwell KL et al. ASCO 2012. Abstract LBA1]. The first interim OS analysis (median OS: CAP plus LAP, 23.3 months; T-DM1 not reached; HR, 0.621; 95% CI, 0.48 to 0.81; p=0.0005) did not cross the efficacy stopping boundary (p=0.0003 or HR=0.617). Dr. Verma presented results of a second interim analysis conducted after 52% of the total targeted number of OS events had been reached. In this analysis, OS significantly favored T-DM1 (30.9 vs 25.1 months; p=0.0006); median follow-up was 19.1 months for T-DM1 and 18.6 months for CAP plus LAP. The OS benefit was observed in most subgroups, including line of metastatic therapy (1st, 2nd, 3rd, or later), ER/PR status, and age, although the subgroup of patients aged >75 years was too small to confirm benefit. The secondary endpoints of objective response rate and duration of response also favored T-DM1.

Approximately 53% of CAP patients and 27% of LAP patients required a dose reduction compared with 16% of T-DM1 patients. T-DM1 was well tolerated and associated with fewer grade ≥3 adverse events (40.8% vs 57.0%), except for thrombocytopenia (12.9 % vs 0.2%), increased serum aminotransferase levels, and anemia. Adverse events leading to treatment discontinuation were higher for CAP plus LAP (10.7%) patients relative to T-DM1 (5.9%) patients. The rates of cardiac dysfunction adverse events were low and similar in both arms.

The study researchers concluded that T-DM1 should offer an important therapeutic option in the treatment of HER2-positive metastatic breast cancer patients. Final OS analysis (descriptive only) is expected in 2014.

Phase 3 Study of Crizotinib Versus Pemetrexed or Docetaxel Chemotherapy in Patients with Advanced ALK-Positive NSCLC

Written by ***Toni Rizzo***

Although single-agent second-line chemotherapy has limited efficacy in unselected non-small cell lung cancer (NSCLC), its effect in advanced anaplastic Kinase positive (ALK+) NSCLC is uncertain. Crizotinib has marked clinical activity in ALK+ NSCLC [Camidge DR et al. *Lancet Oncol* 2012; Kim DW et al. ASCO 2012. Abstract 7533]. The PROFILE 1007 [NCT00932893] trial, presented by Alice Tsang Shaw, MD, PhD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, compared the efficacy and safety of crizotinib with standard chemotherapy as second-line therapy in patients with advanced ALK+ NSCLC.

A total of 347 patients with previously treated stage IIIB/IV ALK+ NSCLC were randomized to crizotinib (250 mg BID, orally, 21-day cycle; n=173) versus pemetrexed