The UK START Trials: 10-Year Follow-Up Results

Written by Toni Rizzo

The international standard for radiotherapy after primary surgery for early breast cancer has been a total dose of 50 Gy administered in 25 small daily fractions over 5 weeks. However, the randomized UK Standardisation of Breast Radiotherapy [START] trials indicate that a lower total dose delivered in fewer larger fractions is likely to be safe and effective [START Trialists' Group. *Lancet* 2008; *Lancet Oncol* 2008]. The 5-year results of the START B trial suggested that 40 Gy in 15 fractions is as safe as and noninferior in terms of tumor control to 50 Gy in 25 fractions [START Trialists' Group. *Lancet* 2008]. John Yarnold, MBBS, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom, presented the 10-year follow-up results of the UK START trials, which tested 13- and 15-fraction regimens in women with completely excised early breast cancer (T1-3, N0-1, M0). The START trials were coordinated by the Clinical Trials and Statistics Unit at The Institute of Cancer Research and funded by Cancer Research UK, the UK Medical Research Council, and the UK Department of Health.

In Trial A, 2236 patients were randomized to receive 50 Gy in 25 fractions (n=749), 39.0 Gy in 13 fractions (n=737), or 41.6 Gy in 13 fractions (n=750), all given for 5 weeks [START Trialists' Group. *Lancet Oncol* 2008]. In Trial B, 2215 patients were randomized to 50 Gy in 25 fractions for 5 weeks (n=1105) or 40 Gy in 15 fractions for 3 weeks (n=1110) [START Trialists' Group. *Lancet* 2008]. The primary endpoint was local-regional relapse. Secondary endpoints included effects on normal tissue, disease-free survival, and overall survival. The median follow-up was 9.3 years for Trial A and 9.9 years for Trial B.

In Trial A, the 10-year rate of patients with local-regional relapse was 7.4% (95% CI, 5.5 to 10.0) after 50 Gy, 6.3% (95% CI, 4.7 to 8.5) after 41.6 Gy, and 8.8% (95% CI, 6.7 to 11.4) after 39 Gy. The hazard ratio (HR) for 41.6 versus 50 Gy was 0.91 (95% CI, 0.59 to 1.38) and for 39 versus 50 Gy was 1.18 (95% CI, 0.79 to 1.76). In Trial B, the percentage of patients with a local-regional relapse was 5.5% (95% CI, 4.2 to 7.2) after 50 Gy and 4.3% (95% CI, 3.2 to 5.9) after 40 Gy. The HR for 40 vs 50 Gy was 0.77 (95% CI, 0.51 to 1.16).

Trial A results showed similar rates of moderate/marked adverse effects on conserved breast tissue with 41.6 versus 50 Gy (HR, 0.94; 95% CI, 0.79 to 1.11) and suggested lower rates with 39 versus 50 Gy (HR, 0.80; 95% CI, 0.67 to 0.96). In Trial B the rates were lower with 40 versus 50 Gy (HR, 0.77; 95% CI, 0.66 to 0.89).

The UK START 10-year results indicate that patients can be safely and effectively treated with a lower total dose with fewer fractions than the historical standard of 50 Gy per 25 fractions. No detrimental effects of hypofractionation were identified in patient subgroups, including age <50 or >50 years, type of primary surgery, axillary node status, tumor grade, whether a tumor-bed boost was given, and treatment with adjuvant chemotherapy. These results support the use of 40 Gy in 15 fractions as the UK standard for patients with early invasive breast cancer after breast-conserving surgery or mastectomy, as recommended in the *NICE Clinical Guidelines, No. 80* [National Institute for Health and Clinical Excellence 2009] and supported by the advice given in the American Society for Radiation Oncology guidelines for fractionation in whole-breast irradiation (for patients not receiving a tumor-bed boost) [Smith BD et al. *Int J Radiat Oncol Biol Phys* 2010].

HERA TRIAL: 2 Years Versus 1 Year of Trastuzumab After Adjuvant Chemotherapy in Women with HER2-Positive Early Breast Cancer at 8 Years of Median Follow-Up

Written by Emma Hitt, PhD

In 2005, data from 3 large randomized trials demonstrated that 1 year of trastuzumab treatment provided a statistically significant disease-free survival (DFS) benefit compared with no trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer [Piccart-Gebhart MJ et al. *N Engl J Med* 2005]. One of these studies, the Trastuzumab in Treating Women with Primary Breast Cancer [HERceptin Adjuvant (HERA); NCT00045032] trial, continued trastuzumab therapy to assess whether 2 years of treatment was superior to 1 year. Martine J. Piccart-Gebhart, MD, PhD, Jules Bordet Institute, Brussels, Belgium, provided an update of the HERA trial after 8 years of median follow-up.

Women with locally determined and centrally confirmed early HER2-positive invasive breast cancer who had undergone surgery and neoadjuvant chemotherapy with or without radiation therapy were recruited globally except in the United States (n=5102). Patients were randomized to observation, 1 year of trastuzumab every 3 weeks, or 2 years of trastuzumab every 3 weeks. Patients in the observation arm were given the option of crossing over after the release of first results in 2005.

No significant difference was found in DFS or overall survival (OS) between the 2- and 1-year trastuzumab arms at 8 years median follow-up. When patients were stratified