One year (yr) of trastuzumab (TR) significantly improves disease-free (DFS) and overall survival (OS) in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC) and is considered the standard of care. The HERA randomized trial investigated whether longer duration of TR can further improve outcome. HERA (BIG 01–01) is an international, multicentre, Phase III randomized trial involving 5102 women with HER2-positive EBC. Patients were randomized, after completion of primary therapy (surgery, chemotherapy and radiotherapy as indicated), to TR every 3 weeks for 1 yr, 2 yrs, or to observation. This landmark efficacy analysis compares the outcome of patients who were disease-free at 1 yr after randomization and who were randomized to 2 yrs or 1 yr of TR (N=1553 for 2 yrs, and N=1552 for 1 yr). The primary endpoint is DFS and secondary endpoints are OS and time to distant recurrence (TTDR). Updated efficacy analyses of the TR arms vs observation at 8-yr median follow-up (FU) are also presented.

In April 2012, HERA reached the target number of 725 DFS events needed for 80% power to detect a true hazard ratio (HR) of 0.80 for the comparison of 2 yrs vs 1 yr of TR. The unadjusted HR for an event in the 2-yr vs 1-yr TR arms was 0.99 (95% CI 0.85–1.14; p=0.86). OS in the two arms was comparable [HR=1.05; 95% CI 0.86–1.28; p=0.63]. TTDR results were similar. The primary cardiac endpoint was comparable (1.0% vs 0.8% for 2-yr and 1-yr arms, respectively), but the secondary cardiac endpoint** was higher in the 2-yr arm (7.2% vs 4.1%). Importantly, the durable benefit in DFS and OS for both 1 yr and 2 yrs of TR compared with observation remained stable at 8 yrs of median FU.

These results confirm that 1 yr of adjuvant TR remains the standard of care for HER2-positive EBC pts. The significant improvement in DFS and OS persists over time and the incidence of cardiac endpoints remains low at a median FU of 8 yrs.

One year of adjuvant trastuzumab (TR) has been providing survival benefit to patients with early HER2-positive breast cancer since the results of adjuvant trials were first put into practice in 2005. But the optimal duration of TR has been debatable due to cardiac toxicity concerns and results from the FinHer trial, which showed that 9 weeks of TR provided a similar magnitude of benefit as 1 yr, albeit in a very small trial. The French National Cancer Institute (INCa) initiated an academic randomized non-inferiority trial to compare a shorter TR exposure of 6 months vs the standard 12 months. This trial was named PHARE for “Protocol for Herceptin as Adjuvant therapy with Reduced Exposure” [NCT00381901].

Patients with HER2+ early breast cancer who received at least 4 cycles of (neo)adjuvant chemotherapy were eligible. Randomization was 1:1 using a minimization algorithm; subjects were stratified for concomitant vs sequential TR administration with chemotherapy, estrogen receptor (ER) status and centre. The primary objective was to compare disease-free survival (DFS). Overall survival (OS) and cardiac toxicity were investigated as secondary aims. An absolute difference of 2% in DFS was defined as the non-inferiority margin (with a lower boundary for the hazard ratio of 1.15) and required 3400 patients with alpha=0.05 and 80% power.

From 2006 to 2010, 3382 patients were randomized to 6 or 12 months of TR. Disease and treatment characteristics were well balanced between the 2 arms: median age 55 years (range 21–86 years), median tumour size 20 mm (range 0–270 mm), node involvement 45%, Scarff-Bloom-Richardson (SBR) Grade III 56%, ER-positive 58%, radiotherapy 88%, concomitant TR administration 58%, anthracycline- and taxane-containing chemotherapy 73%. The database was locked on July 30, 2012. The hazard ratio (HR) was 1.28 with 95% HR confidence intervals of 1.09 and 1.66 for DFS. As the 95% confidence interval crossed the prespecified lower boundary of 1.15, the trial was deemed inconclusive, and non-inferiority could not be established. In terms of DFS events, the 6-month arm had 13% while the 12-month arm had 10.4%.

** LVEF < 50% and 10% below baseline confirmed by repeat assessment, excluding patients with a primary cardiac endpoint.

* NYHA class III or IV, confirmed by a cardiologist, and LVEF < 50% and 10% below baseline, OR cardiac death.

TRIAL SUMMARY: Second year of trastuzumab brings no clear added benefit in HER2+ early disease

TRIAL SUMMARY: Inconclusive results on shortened course of adjuvant trastuzumab
COMMENTARY: There is a long history in the development of cancer therapy of establishing a “foundation regimen” and then trying to either add to or chip away at it, to find the perfect balance of efficacy and toxicity. Prolonging or adding to a foundation regimen predominates in diseases with high relapse rates and adverse prognosis. Abbreviating regimens tends to follow the demonstration of high cure rates in a disease, to minimize unnecessary time, cost and toxicity.

These two trials, HERA and PHARE, exemplify this paradigm. The HERA trial was designed at a time when HER2-positive disease was recognized as carrying a poor prognosis, justifying a “more rather than less” strategy. In addition to the observation and 1-year trastuzumab arms, the trial examined 2 years of trastuzumab after chemotherapy, based on the premise that prolonged suppression of the HER2 driver signal might be necessary for a cure. Models for this theory can be found in adjuvant hormone therapy, where longer and longer therapy is associated with better outcomes, and from HER2-positive metastatic trials demonstrating continued response to anti-HER2 therapy after discontinuation of chemotherapy, and through several different disease progression-chemotherapy cycles.

Taking the opposite view, the PHARE trial, designed after adjuvant trials established a much-improved prognosis with adjuvant trastuzumab, explored reducing the duration of trastuzumab from 12 to 6 months. Based on the impressive pathologic complete response rates seen with 3–6 months of neoadjuvant trastuzumab and the high overall survival rates reported in the adjuvant trastuzumab studies, the investigators hypothesized that cure might be achievable with a lot less trastuzumab. Both questions, while working at opposite ends of the paradigm, were rational for the era in which they were conceived.

So what have we learned? After 8 years of followup, HERA results could not identify a benefit from continuing trastuzumab for 2 years; cardiac toxicity, however, was higher in the longer treatment group. While negative results can be anti-climactic, it is reassuring to know that we have not been undertreating women since the introduction of adjuvant trastuzumab in 2005, by stopping after a year of therapy. For patients who become anxious as their year of trastuzumab comes to an end, this is reassuring data. As the cost of cancer care skyrockets, it is also a relief to anyone footing the bill for drugs and resources.

The PHARE trial results require a little more digestion. This trial failed to show that 6 months was equivalent to 12 months of therapy, while not exactly demonstrating that 6 months was inferior. On the one hand, the results upheld 1 year as the standard of care; on the other hand, they provide some reassurance that patients forced to discontinue trastuzumab prematurely may still enjoy a high probability of cure if they have completed at least 6 months. As we have little data on the long-term cardiac safety of trastuzumab, limiting exposure seems wise in patients who exhibit significant toxicity, and this data makes that decision easier. Of interest from PHARE was the confirmation that concomitant (rather than sequential) delivery of chemotherapy and trastuzumab was associated with a smaller difference between the 6- and 12-month treatment groups among the ER-negative subset. The Intergroup study, presented in 2005, previously demonstrated that giving trastuzumab concurrently resulted in statistically fewer relapses than sequential dosing. Whether this reflects synergy of the drugs, or the importance of early introduction of the anti-HER2 drug, remains speculative (it may be both). In any case, the observation from PHARE reinforces our treatment principles on this point also.

Taken together, these two trials strengthen our confidence in the current “foundation regimen”: one year of trastuzumab, beginning during the taxane portion of chemotherapy. For the present this remains the standard of care for what has only recently become a highly curable form of early breast cancer. But HER2-positive breast cancer has been such a fertile research field that questions of duration of TR may soon seem passé. Rapidly accruing and soon-to-start clinical trials are exploring the use of 2 rather than a single anti-HER2 agent with chemotherapy. While neoadjuvant and metastatic trials provide enticing data on the added benefits of doubling up, adjuvant trials are forced to accrue large numbers to detect small differences in DFS, given that long-term followup of adjuvant TR trials already reports astonishingly good results (84% OS at 8 years followup from the combined analysis in a study population that included 9% T3 tumours, 45% estrogen receptor [ER]-negative tumours and 50% younger than 50 years — all adverse prognostic

### IN BRIEF

#### Already known
- One year of adjuvant trastuzumab with chemotherapy results in excellent DFS and OS in patients with HER2-positive breast cancer.

#### What these studies showed
- Lengthening or shortening the duration of trastuzumab cannot be supported.

#### Next steps
- Adjuvant trials are now focusing on adding new anti-HER2 agents to trastuzumab, such as pertuzumab, lapatinib and trastuzumab emtansine (T-DM1).
What does seem certain from cumulative evidence is that trastuzumab is here to stay, and that it has revolutionized the prospects of patients diagnosed with any stage of HER2-positive breast cancer.

**Disclosure:** Dr. Lohrisch reports no conflicts of interest relevant to this article.

**References**