Duration of adjuvant trastuzumab: might less be more?

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The pivotal trials of adjuvant trastuzumab – NSABP B-31, NCCTG N9831, HERA, and BCIRG 006 - which transformed our management of early stage, HER2 positive breast cancer, all deployed one year of adjuvant trastuzumab. Investigators developing these trials knew that the observed synergy between chemotherapy and trastuzumab argued for several months of overlap between the two classes of agents. Beyond that, it was not known when these trials were being developed whether “maintenance” trastuzumab would be valuable, nor what a suitable duration might be. In the end, study sponsors and investigators settled on a total of one year of adjuvant therapy. It proved an inspired, if arbitrary, decision. Among the seminal studies that led to the approval of adjuvant trastuzumab, the Herceptin Adjuvant (HERA) trial was the only study that also evaluated different durations of adjuvant trastuzumab. Results from the HERA trial confirmed that a second year of adjuvant trastuzumab was not superior to the standard one-year regimen. [1] During the same period, results from the Finland Herceptin (FinHER) trial, which included a small subset of HER2+ breast cancer patients, pointed to a significant benefit with a mere nine weeks of adjuvant trastuzumab, implying that the shorter trastuzumab duration might be a useful option.

Multiple randomized studies were designed to test whether shorter treatment durations would be equally effective as the standard 12-month duration of adjuvant trastuzumab among women with HER2 positive, early stage breast cancer. The PHARE, Hellenic Oncology Research Group (HORG), and PERSEPHONE clinical trials compared 6 versus 12 months of adjuvant trastuzumab (see Table). [3-5] The SOLD and Short-HER compared 9 weeks versus 12 months duration (see Table). [6, 7] Each of these trials carried a non-inferiority design; in essence, the studies were powered to show that a shorter duration of treatment would not be inferior to the 12 month standard arm. Investigators conducting non-inferiority studies face considerable challenges inherent to the design of these trials. From a methodological standpoint, the null hypothesis in non-inferiority studies holds that the investigational arm is inferior to the comparator arm. To reject the null hypothesis with a clinically acceptable
inferiority margin, usually within a narrow band of percentage points to the “standard” arm, these studies require larger sample sizes than classical superiority studies. Such sample size considerations make non-inferiority studies less appealing to industry sponsors, and also carry the risk that a statistically “non-inferior” result might still appear numerically inferior, making clinicians and patients squeamish about the non-inferior arm.

The SHORT-HER clinical trial in this issue of the Annals of Oncology randomized 1253 women with HER2 positive breast cancer to a short 9-week treatment of trastuzumab given concurrently with chemotherapy, or to the standard 12 month duration. [7]. In the short-duration arm, trastuzumab was given weekly for nine weeks concomitantly with three cycles of docetaxel. This regimen was followed by three cycles of FEC (5-Fluourouracil, Epirubicin and Cyclophosphamide). In the control arm of the study, patients were treated with four cycles of AC (doxorubicin, cyclophosphamide) or EC followed by four cycles of either paclitaxel or docetaxel. Trastuzumab was administered every three weeks for 18 doses, starting with the first taxane dose. The study primary endpoint was disease-free survival (DFS) with cardiac safety as an important secondary endpoint. Cardiac events were defined as a decrease in the left ventricular ejection fraction (LVEF) > 15 points from baseline or > 10 percentage points drop with absolute value below 50%, or symptomatic congestive heart failure, or any other grade 2 or 3 cardiac events. In order to demonstrate the non-inferiority at pre-specified boundary at 1.29 and with 80% power, the study was planned with a sample size of 2332 patients but due to lower than expected enrollment, the sample size was reduced to 1252 patients. Fifty four percent of the study population was node negative, and 68% hormone receptor positive. The 5-year disease-free survival (DFS) rate in 626 patients who received one year of treatment was 88%, besting the 85% DFS rate among 627 patients who received nine weeks of treatment, yielding a hazard ratio of 1.13 (90% CI 0.89 to 1.42), with the upper limit of the 90% CI crossing the noninferiority margin set at 1.29. In short, Short-HER could not prove non-inferiority for shorter courses of adjuvant trastuzumab. However, the shorter
trastuzumab treatment was also associated with a lower risk of cardiac events (4.3%) compared with 13.1% in the longer treatment regimen. Thus, the Short-HER study suggests trade-offs between reducing the risk of cancer recurrence and incurring the risk of cardiotoxicity with a full year of trastuzumab.

The PHARE, HORG, and SOLD studies also failed to demonstrate non-inferiority. To date, only one of 5 trials of shorter vs longer durations of adjuvant trastuzumab – the PERSEPHONE study of 6 vs 12 months – has demonstrated non-inferiority for a shorter regimen (Table). All the others showed a measurable 2-3% reduction in recurrence risk with the longer duration of trastuzumab therapy. Notably in the PERSEPHONE trial, the subset of patients who received optimal, contemporary patterns of adjuvant treatment including taxane-based chemotherapy and concurrent chemotherapy with trastuzumab actually had a lower risk of recurrence when given the longer, 12 month trastuzumab treatment. At the same time, these trials all show – to varying degrees – higher risks of cardiac events with longer durations of treatment. Fortunately, clinical experience suggests that the risk of trastuzumab-associated cardiac injury is lower with non-anthracycline regimens, and that the vast majority of these instances of cardiotoxicity are asymptomatic changes in left ventricular ejection fraction, which lack important clinical sequelae.

A patient with early stage, HER2 positive breast cancer wants “the best” treatment to prevent cancer recurrence while preserving quality of life and avoiding serious, long-term consequences of therapy. That treatment undeniably includes trastuzumab, given concurrently with taxane-based chemotherapy. The “gains” of longer trastuzumab therapy are quite modest, amounting to single-digit reductions in recurrence rates for women with average risk, HER2 positive tumors. For patients who developed cardiac toxicity or otherwise do not tolerate trastuzumab, or in situations where only shorter durations of trastuzumab are available, it seems clear that the “lion’s share” of benefit is achievable with
6 months of treatment. But based on the data in Short-HER2 and four other trials of treatment duration, we believe that 12 months of trastuzumab, including 3 months of concurrent administration with taxane-based chemotherapy, remains the standard of care and the optimal duration of therapy. Lesser durations of trastuzumab maintenance treatment appear associated with a greater risk of disease recurrence. Finally, in cases of higher risk, HER2 positive breast cancer, current treatment standards may include additional anti-HER2 therapies such as pertuzumab or neratinib. We note that there are simply no data that these interventions benefit women who received less than 12 months of trastuzumab.

One year is a long time, especially when getting treatment for breast cancer. But for most women with HER2 positive tumors, that looks like time well spent.
Table. Non-inferiority studies designed comparing 12 months to shorter durations of adjuvant trastuzumab

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Randomization of 12 m trastuzumab vs</th>
<th>Δ absolute rate of cardiac toxicity* % with longer duration</th>
<th>Δ DFS absolute benefit % for longer duration</th>
<th>HR</th>
<th>Non-inferior (NI)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARE [3]</td>
<td>3384</td>
<td>6 m</td>
<td>3.8%</td>
<td>2.6%</td>
<td>1.28</td>
<td>Not NI</td>
</tr>
<tr>
<td>HORG [4]</td>
<td>481</td>
<td>6 m</td>
<td>0.0%</td>
<td>2.4%</td>
<td>1.57</td>
<td>Not NI</td>
</tr>
<tr>
<td>PERSEPHONE [5]</td>
<td>4088</td>
<td>6 m</td>
<td>4.0%</td>
<td>0.4%</td>
<td>1.07</td>
<td>NI</td>
</tr>
<tr>
<td>SOLD [6]</td>
<td>2174</td>
<td>9 w</td>
<td>0.9%</td>
<td>2.5%</td>
<td>1.39</td>
<td>Not NI</td>
</tr>
<tr>
<td>SHORT-HER [7]</td>
<td>1254</td>
<td>9 w</td>
<td>8.8%</td>
<td>3.0%</td>
<td>1.13</td>
<td>Not NI</td>
</tr>
</tbody>
</table>

*studies differed with respect to definitions for cardiotoxicity
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5. Earl HM, Hiller L, Vallier A-L et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. Journal of Clinical Oncology 2018; 36: 506-506.