Adjuvant Trastuzumab: Does Time Really Matter?

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The U.S. Food and Drug Administration (FDA) initially approved trastuzumab for the treatment of patients with HER2-positive metastatic breast cancer in September 1998. This approval marked the beginning of an era of extremely effective treatment for women with a form of breast cancer previously associated with very poor outcomes [1]. Subsequent large trials initiated in 2000 and 2001 produced stunning results that led to the 2006 approval of trastuzumab in the adjuvant setting by the European Medicines Agency and FDA, with an updated approval for use in combination with docetaxel and carboplatin in 2008 [2–6]. Trastuzumab is now the standard of care for metastatic and early breast cancer; however, questions remain regarding the optimal schedule of trastuzumab in the adjuvant setting. First and most importantly, the optimal duration of trastuzumab treatment is still unknown. Second, it is unclear whether there is a benefit to providing trastuzumab sequentially versus concurrently to chemotherapy.

The six initial adjuvant trials included the Herceptin Adjuvant (HERA) trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial, the North Central Cancer Treatment Group (NCCTG) N9831 trial, the Breast Cancer International Research Group 006 trial, Fédération Nationale des Centres de Lutte Contre le Cancer PACS04 trial, and the Finnish study FinHer [2–5, 7]. Each of these trials compared chemotherapy with and without trastuzumab. The NSABP B-31 and NCCTG N9831 trials had similar designs, which allowed results to be reported as a joint analysis. In all but one of the initial studies, trastuzumab was given for 1 year either concurrently or sequentially to chemotherapy. The choice to treat with 1 year of trastuzumab was initially arbitrary, so it is possible that a shorter duration of trastuzumab could be equally effective, with reduced costs, better convenience, and less cardiac toxicity. The FinHer trial was the only one to administer trastuzumab for less than 1 year [7]. In that study, 9 weeks of trastuzumab provided a similar benefit as 1 year of trastuzumab; however, it was a small trial, and further studies are needed to validate the results. Several studies have since been initiated: the Protocol for Herceptin as Adjuvant Therapy With Reduced Exposure (PHARE) trial; Persephone, a Hellenic Cooperative Oncology Research Group study; the Synergism Or Long Duration (SOLD) study; and the Short-HER trial (Table 1) [8–12]. Results from these trials, as well as the ongoing HERA trial, should help to determine the optimal duration of trastuzumab therapy. In the meantime,

HERA and PHARE recently reported 8- and 4-year results, respectively [13, 14].

The HERA trial addressed the issue of longer-term trastuzumab therapy [13]. In this trial, 5,102 women with HER2-positive early breast cancer were randomized to trastuzumab every 3 weeks for 1 or 2 years or to observation only after completion of primary therapy. The 8-year analysis showed that disease-free survival (DFS) rates were the same for the 1- and 2-year treatment arms, 76% versus 75.8%, respectively, with a hazard ratio (HR) of 0.99, suggesting that 1 year of trastuzumab should continue as the standard of care. In the 4-year subgroup analysis, a slight benefit was observed for patients with hormone receptor-negative breast cancer who received 2 years of trastuzumab; however, the 8-year analysis showed that the advantage was only transient, with no difference in DFS rates for 1 year versus 2 years of trastuzumab, regardless of hormone-receptor status [13]. The results highlight the need for long-term follow-up, even in an aggressive disease such as HER2-positive breast cancer. Severe cardiac toxicity was uncommon in the HERA study, 0.1% and 0.8%, for 1 year and 2 years of trastuzumab, respectively, and 1.0% for observation only. These rates were much lower than those reported in the 7-year analysis of NSABP B-31: 4.0% versus 1.3% for the trastuzumab arm and control arms, respectively [15]. However, the definitions of cardiac toxicity between these studies were not the same, so comparisons should be performed with caution.

The PHARE trial addressed the use of trastuzumab for less than 1 year [14]. In this trial, 3,480 patients with HER2-positive early breast cancer were randomized to 6 or 12 months of trastuzumab concomitantly or sequentially with chemotherapy. PHARE was a noninferiority trial designed to detect a 2% difference in recurrence. The predefined noninferiority margin was 1.15; therefore, the 6-month regimen would be noninferior to the standard 12-month regimen if the confidence interval did not include 1.15 and the upper limit of the confidence interval was less than 1.15. Results from the intent-to-treat analysis showed that the 4-year DFS rates for 6 months versus 12 months of trastuzumab were 84.9% and 87.8%, respectively, with a HR of 1.28 and a confidence interval (CI) of 1.05–1.56 [14]. Because the CI contained the 1.15 noninferiority margin, results were inconclusive. Nonetheless, a HR of 1.28 suggests a benefit favoring 12 months' duration of trastuzumab. More cardiac events were reported in the 12-month arm than the 6-month arm (5.7% vs. 1.9%; $p < .0001$), demon-

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Table 1. Adjuvant trastuzumab breast cancer trials

Study	Trastuzumab duration	Follow-up period (yr)	Hazard ratio DFS	Treatment order	Nodes
Adjuvant trials					
BCIRG 006 [4]	0 vs. 1 yr	5	0.64	Concurrent	+/-
ACTH		5	0.75		
TCH					
FinHER [6, 7]	0 vs. 3 mo	3	0.42 (RFS)	Concurrent	+/-
		5	0.65 (DDFS)		
FNCLCC PACS04 [5]	0 vs. 1 yr	4	0.86	Sequential	+
HERA [2, 13]	0 vs. 1 yr	4	0.76	Sequential	+/-
	0 vs. 1 yr	8	0.76		
NSABP B31/NCCTG N9831 [17]	0 vs. 1 yr	4	0.52	Concurrent arms only	+/-
NSABP B31/NCCTG N9831 [24]	0 vs. 1 yr	10	0.60	Concurrent arms only	
NCCTG N9831 [16]	0 vs. 1 yr	4	0.67	Sequential arm	+/-
Duration trials					
HERA [13]	1 vs. 2 yr	8	0.99	Sequential	+/-
PHARE [14]	6 mo vs. 1 yr	4	1.28	Concurrent/sequential	+/-
Ongoing duration trials					
Study	Trastuzumab duration	Target enrollment	Accrual	Treatment order	Nodes
Hellenic [10]	6 mo vs. 1 yr	500	478	Concurrent	+
Persephone [9]	6 mo vs. 1 yr	4,000	2334	Concurrent/sequential	+/-
SOLD [11]	3 mo vs. 1 yr	3,000	1538	Concurrent	+/-
ShortHER [12]	3 mo vs. 1 yr	2,500	1070	Concurrent	+/-

Abbreviations: A, doxorubicin; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; DDFS, distant disease-free survival; DFS, disease-free survival; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; H, trastuzumab; HERA, Herceptin Adjuvant; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; PHARE, Protocol for Herceptin as Adjuvant Therapy With Reduced Exposure; RFS, relapse-free survival; T, docetaxel.

strating a significant benefit in terms of cardiac safety with less trastuzumab exposure.

If the other duration studies show that 12 months of trastuzumab is more effective than 6 months, as the trend suggests in PHARE, we must ask why longer exposure to trastuzumab is better. A closer evaluation of these trials provides insight into this as well as the question of sequential versus concurrent trastuzumab. In PHARE, 58% of patients received trastuzumab concurrently. Exploration of the data by subgroups reveals a DFS HR for concurrent therapy of 1.15 (95% CI: 0.87–1.53) compared to 1.41 (95% CI: 1.06–1.86) for sequential therapy [14]. The 1.15 HR is the same as 1.15 HR required to show noninferiority for 6 versus 12 months. Although this analysis is subject to multiple testing, it poses the question of whether trastuzumab treatment given concurrently for a shorter duration could be as beneficial as 1 year of treatment. It would be worthwhile to pursue this observation in an analysis overview of trial data over a longer follow-up period.

Further examination of other trastuzumab trials also suggests that sequential therapy may be less effective than concurrent. Both HERA and PHARE included sequential therapy (100% sequential in HERA and 42% sequential in PHARE). The HRs for sequential studies are generally higher, indicating less of a benefit than HRs for concurrent studies. In the HERA sequential study, the 8-year DFS HR was 0.76 for 1 year of treatment versus none, and the HR from the NCCTG N9831 arm also comparing 1 year of sequential trastuzumab to none was

0.67 [13, 16]. Data comparisons are shown in Table 1. Both of these HRs are higher than the HR of 0.60 from the joint NSABP B31/NCCTG 9831 analysis, which contained only concurrent arms [17]. This assessment, along with preclinical data, suggests that optimal efficacy may require concurrent treatment with chemotherapy [18]. However, cross-study comparisons are not wise. The differences could be due to the fact that more node-negative patients with lower risk of recurrence were enrolled in the HERA trial (33%) compared to the joint B-31/N9831 analysis (10%). It could also be due to the high number of patients (50%) in HERA who crossed over to trastuzumab from the control arm after the first interim analysis.

Results from HERA and PHARE indicate that 12 months of trastuzumab is more effective than 6 months and 12 months is as effective as 2 years; therefore, 1 year of adjuvant trastuzumab remains the standard of care. It is very important, however, that the PHARE data is peer-reviewed and a longer follow-up obtained before final conclusions are made. An overview of the raw data from all the trastuzumab duration trials could answer questions such as whether concurrent versus sequential therapy is more beneficial. There are many exciting ongoing trastuzumab trials, including treatment combinations with lapatinib (ALTTO) [19], bevacizumab (BETH) [20], and pertuzumab (APHINITY) [21]. A study evaluating pertuzumab with or without trastuzumab emtansine will begin accruing patients soon.

Other questions remain unanswered with regard to trastuzumab therapy. What is the optimal chemotherapy partner for trastuzumab? Is there a group of patients with HER2-positive breast cancer who should receive only trastuzumab? The NeoSphere and TBCRC 006 trials have reported high pathologic complete response rates in patients with HER2-positive tumors treated only with targeted therapies, suggesting that there is a group of patients who may do well without the use of chemotherapy [22, 23]. These patients need to be identified. Results from these and other trials will help to answer these questions, providing significant treatment advances for patients with HER2-positive breast cancer.

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