

Why Your Preferred Targeted Drugs May Become Unaffordable

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Abstract

Trastuzumab, a monoclonal antibody directed at the HER2 receptor, is one of the most impressive targeted drugs developed in the last two decades. Indeed, when given in conjunction with chemotherapy, it improves the survival of women with HER2 positive breast cancer, both in advanced and in early disease. Its optimal duration, however, is poorly defined in both settings with a significant economic impact in the adjuvant setting where the drug is arbitrarily given for 1 year. This article reviews current attempts at shortening this treatment duration, emphasizing the likelihood of inconclusive results and, therefore, the need to investigate this important variable as part of the initial pivotal trials and with the support of public health systems. Failure to do so has major consequences on treatment affordability. Ongoing adjuvant trials of dual HER2 blockade, using trastuzumab in combination with a second anti-HER2 agent, and trials of the antibody–drug conjugate T-DM1 (trastuzumab–emtansine) have to all be designed with 12 months of targeted therapy. *Cancer Res*; 73(19); 5849–51. ©2013 AACR.

Advances in Targeted Treatment Approaches for Women with HER2-Positive Breast Cancer

Trastuzumab is the foundation of care of women with HER2 positive breast cancer, given its profound impact on the natural history of this disease, which is much less feared by oncologists than two decades ago. Survival rates have markedly improved in the metastatic setting, whereas cure rates are enhanced in the adjuvant setting (1).

Three additional anti-HER2 agents are now Food and Drug Administration-approved for advanced disease patients: lapatinib, a dual EGFR/HER2 reversible tyrosine kinase inhibitor (TKI), is approved in combination with either capecitabine or letrozole (2, 3); pertuzumab, a monoclonal antibody binding to the dimerization domain of HER2 and preventing ligand-induced HER2–HER3 dimerization, is approved for use in the first line setting of HER2-positive metastatic breast cancer (MBC), in combination with trastuzumab and docetaxel (4); finally, the antibody–drug conjugate T-DM1, consisting of a potent maytansinoid antimicrotubule agent bound to trastuzumab through nonreducible thioether bonds, is a new approved option for women with advanced disease previously exposed to trastuzumab, in view of its superior activity/toxicity profile when compared with the combination of capecitabine and lapatinib (5).

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The duration of anti-HER2 therapy in advanced disease

Two randomized clinical trials have attempted to define the benefit—if any—of continuing anti-HER2 therapy beyond progression on a first-line trastuzumab-containing regimen given for MBC. Both did show a benefit in terms of progression-free survival (PFS) for either the continuation of trastuzumab (in the trial of capecitabine with or without prolongation of trastuzumab; ref. 6) or for the switch from trastuzumab to lapatinib (in the trial of capecitabine with or without lapatinib; ref. 2). HRs for PFS were 0.69 [95% confidence interval (CI), 0.48–0.97; $P = 0.0338$] and 0.47 (95% CI, 0.33–0.67; $P < 0.001$), translating into prolongation in median PFS of 2.6 and 4.0 months, respectively (2, 6).

As a result, most oncologists support continued HER2 blockade, even beyond progression in the setting of HER2-positive MBC. However, none of these two trials was powered for detecting an overall survival improvement, and predictive biomarkers to define the subset of patients deriving clinical benefit from this strategy involving high financial costs are lacking.

The duration of anti-HER2 therapy in early disease

The pivotal adjuvant trastuzumab trials—namely the HERA and the NSABP-B31 pooled with NCCTG-9831—all selected in an arbitrary fashion, a 1-year trastuzumab duration of administration given either in sequence with chemotherapy or with a partial overlap (7, 8). The only weak rationale behind this choice was the fact that initial trials of adjuvant tamoxifen had tested a 1-year duration of anti-estrogen therapy versus placebo (9). Convinced that the principle "the longer the better," shown to be valid for adjuvant tamoxifen (10), was also going to apply to adjuvant anti-HER2 therapy, HERA clinical investigators insisted on having a 2-year trastuzumab duration arm in their trial, which was accepted by the pharmaceutical sponsor, Roche.

The comparison of 2 years versus 1 year of trastuzumab involved a landmark analysis of 3,105 patients that were disease free at 12 months after randomization to 1 of the 2 trastuzumab arms. Because this analysis was event-driven rather than time-driven and because it was planned after at least 725 primary endpoints (recurrence of breast cancer, contralateral breast cancer, second primary malignancy, or death), it took 7 extra years after the release of the positive results of the 1-year arm versus the observation arm (in 2005) to find out that 2 years did not provide any disease-free survival or overall survival advantage (HR = 0.99 and 1.05, respectively) over 1 year but did induce a higher rate of grade 3 or 4 adverse events as well as more asymptomatic or mildly symptomatic cardiac events (11).

Back in 2006, a small academic-led adjuvant trial, conducted in Finland, attracted a lot of attention (12). This trial showed, in 232 patients with HER2 positive breast cancer, a statistically significant benefit in terms of 3-year recurrence-free survival (HR = 0.42; 95% CI, 0.21–0.83; *P* = 0.01) from only 9 weeks of trastuzumab compared with no trastuzumab, which was similar to the magnitude of benefit seen in the pivotal trials. The unique design of this trial deserves some comments. Contrary to all other adjuvant trastuzumab trials, the monoclonal antibody was given upfront for 9 weeks in combination with either docetaxel or vinorelbine (every 3 weeks for 3 courses) and this highly synergistic combination was then followed by 3 courses of an anthracycline-based regimen (5-fluorouracil,

epirubicin, and cyclophosphamide) administered with residual trastuzumab concentrations in the circulation, given the rather long half-life of trastuzumab (28.5 days, 95% CI, 25.5–32.8 days; ref. 13).

It is tempting to speculate that this particular sequence of drug administration might account for the powerful anti-tumor effect observed and render a prolonged targeted therapy superfluous. Currently, the Finnish investigators are conducting a large randomized trial [the Synergism Or Long Duration (SOLD) study/NCT00593697] to compare their 9 week trastuzumab regimen with one year of trastuzumab therapy. Here the plan is to recruit 3000 patients with the help of several other countries. The trial is half way completed, but its accrual suffers from competitive parallel trials testing dual HER2 blockade in the adjuvant setting; furthermore, there is a legitimate concern about patient selection factors that might direct the lower risk patients to SOLD and the higher risk patients to the competitive trials. This could markedly delay the final analysis of SOLD and render its results obsolete.

As shown in Fig. 1, there are several other randomized adjuvant trials investigating shorter durations of trastuzumab. The SHORT-HER2 trial, conducted in Italy, evaluates 9 weeks versus 12 months of trastuzumab and is prematurely closed with 1,250 patients. Three other national trials compare 6 versus 12 months of trastuzumab. The Hellenic Oncology Research Group trial (NCT00615602) is closing accrual earlier

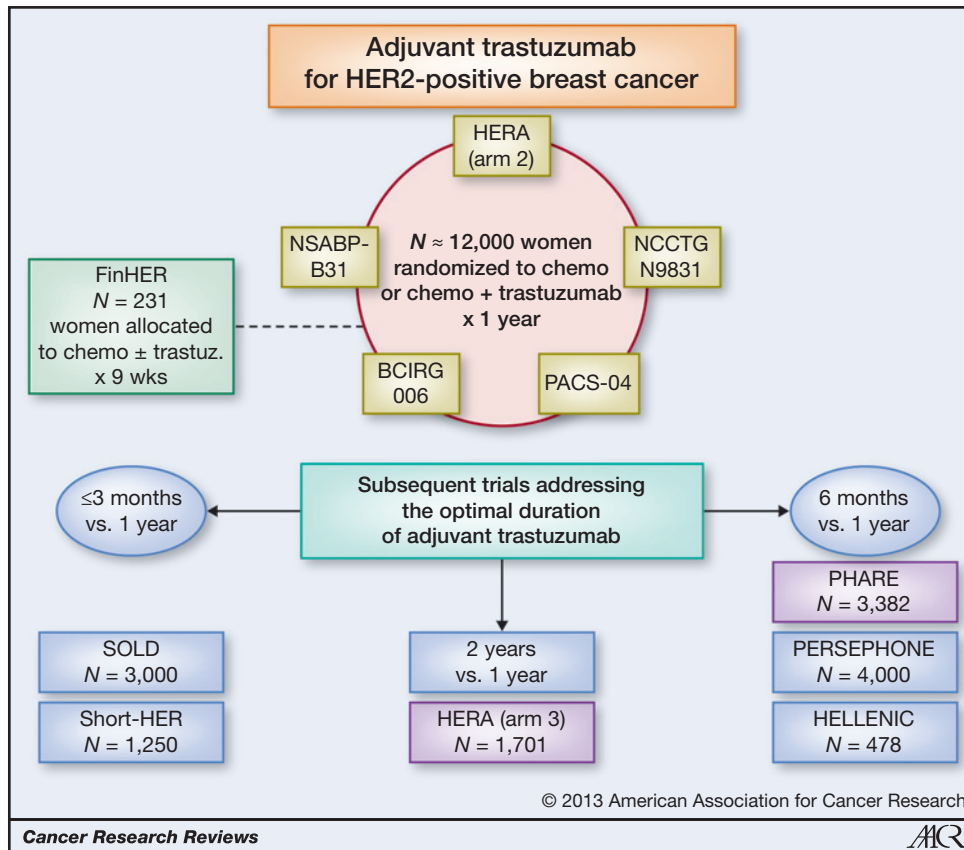


Figure 1. Randomized adjuvant trials investigating shorter durations of trastuzumab.

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than foreseen with an estimated enrollment of 478 patients. The PERSEPHONE trial (NCT00712140), having a planned total enrollment of 4,000 patients, is actively but slowly recruiting in the UK. The PHARE trial (NCT00381901), an academic randomized, noninferiority trial run by the French National Cancer Institute, has released its first results pertaining to 3,382 patients randomized and followed for a median of 42.5 months. PHARE failed to show that 6 months of trastuzumab is noninferior to 12 months (HR = 1.28; 95% CI, 1.09–1.66, $P = 0.29$ for a noninferiority HR of 1.15; 14).

The Heavy Implications for the Public Health Systems of Omitting a Proper Pivotal Clinical Trial Design Investigating the Optimal Duration of Targeted Drugs

It is ironic that governments outside the United States do not care about the design and conduct of the large registration trials that are changing clinical practice. The whole financial burden of those and most of the scientific responsibility lay in

the hands of pharmaceutical industry. For obvious reasons, the latter is reluctant to take "risks" with shorter treatment durations and often selects the duration that will secure "return on investment." This trend could worsen in the future as companies will face increasing stratification of cancer patient populations in the era of next generation sequencing and decreasing hope for a "blockbuster drug." Academic investigators have very little power to influence these business decisions, which may lead to overtreatment of many patients and rapidly escalating costs.

The history of the adjuvant trastuzumab trials illustrates—in a powerful way—the "impossible mission" of treatment de-escalation. This story also calls for the urgent need of contribution of governments in the phase III trials that have the potential to change clinical practice. Failure to do so is a major threat to "affordable" cancer care in the emerging era of "personalized medicine."

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