Her2 (erbB2) receptor is overexpressed in around twenty percent of early breast cancer and historically conferred a poorer prognosis (1). Targeted anti-Her2 therapy has significantly improved outcomes for these women. The current standard of care is chemotherapy with twelve months of trastuzumab, a monoclonal antibody against the extracellular domain of Her2, with four randomized controlled trials showing substantially improved disease-free survival and overall survival and combined analysis of two trials (National Surgical Adjuvant Breast and Bowel Project [NSABP] trial B-31 and North Central Cancer Treatment Group [NCCTG] trial N9831) showing a statistically significant, 33% reduction in mortality (2-5). In early results from the HERA trial, 1 year of trastuzumab versus placebo after standard neoadjuvant or adjuvant chemotherapy improved overall survival with a hazard ratio of 0.66 (95% CI, 0.47-0.91). The hazard ratio on longer follow up was attenuated by the effect of 52% cross over from the control group after interim reporting and longer follow up (5). Trastuzumab is generally well tolerated but as with other Her2 targeted therapy, is associated with asymptomatic reduction in left ventricular ejection fraction, and rarely, congestive cardiac failure. Recent evidence suggests using a non-anthracycline containing combination reduces this risk without significantly affecting outcomes (4).

Lapatinib in early Her2 positive breast cancer

Lapatinib, an oral tyrosine kinase inhibitor against intracellular pathways activated by Her1 (EGFR) and Her2, has shown activity as a single agent in second-line treatment of metastatic Her2 positive breast cancer, in combination with capecitabine and in combination with letrozole. In addition to cardiotoxicity, the major potential adverse effects include diarrhea and hepatotoxicity.

The combination of lapatinib and trastuzumab is more effective than trastuzumab or lapatinib alone in the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (Neo-ALLTO) study (6), which randomized 455 patients with locally advanced (>2 cm) Her2+ breast cancer to 3 treatments arms: oral lapatinib (1,500 mg/d), weekly trastuzumab, or lapatinib (1,000 mg/d later amended to 750 mg/d) plus trastuzumab. The Her2-targeted therapy was given alone for 6 weeks and then with weekly paclitaxel for 12 weeks until surgery. Four cycles of FEC (5-fluorouracil, epirubicin, and cyclophosphamide), followed by 34 weeks on the same Her2-targeted treatment were given after surgery. The rate of pathologic complete response (pCR) for the combination group was 51.3%, almost double the pCR of the trastuzumab and lapatinib alone groups, 29.5% and 21.1% respectively.

Single agent lapatinib did not meet criteria for non-inferiority to trastuzumab in the adjuvant ALLTO trial and the lapatinib arm was discontinued at interim safety analysis (7). In the GeparQuinto trial, HER-2 positive patients who did not achieve pathologic complete response after 4 cycles of Epirubicin and Cyclophosphamide (EC) with or without bevacizumab were randomized to EC docetaxel with or without either trastuzumab or lapatinib. In 270 treated patients, pCR was 31.3% in the trastuzumab arm compared with 21.3% in the lapatinib arm (8).

Neoadjuvant and adjuvant trials have been consistent in finding a weaker therapeutic index for lapatinib relative to trastuzumab, and thus it is not recommended as anti-Her2 therapy in the curative treatment of breast cancer as a single agent alternative to trastuzumab. Even as an adjunctive therapy in combination with trastuzumab, the additional cost and toxicity makes it less likely that such as strategy will
be adopted as a standard of care without the identification of subgroups for whom the additional risks are justified. Long term follow up of the combination in the adjuvant setting is awaited.

Recently, Goss and colleagues (9) have reported mature results of a randomized controlled trial of adjuvant lapatinib, as a single agent, in trastuzumab naïve women previously treated with chemotherapy alone for early stage Her2 overexpressing breast cancer. The study was conceived at a time when adjuvant trastuzumab was available to relatively few women and patients were enrolled between 2006-2008. The majority of patients had T2 or greater disease, and 54% were node positive. Although the total cohort of 3,147 women intention to treatment analysis did not show a significant difference between 1500mg per day of lapatinib for twelve months versus placebo (HR 0.83; 95% CI, 0.70-1.00; P=0.053), central review confirmed Her2 positivity of only 79% of cases. Analysis of this true Her2 positive subgroup did find a statistically significant difference in the hazard ratio for the primary endpoint of disease free survival (HR 0.82; 95% CI, 0.67-1.00; P=0.04). Variability in local testing and tumor heterogeneity are well recognized as potentially impacting efficacy endpoints (10,11).

In pre-specified subgroup analyses, a significant benefit of twelve months lapatinib versus placebo was apparent for hormone receptor negative patients (HR 0.68; 95% CI, 0.52-0.89; P=0.006) but not in those with oestrogen or progesterone receptor positive tumors (HR 0.98; 95% CI, 0.77-1.25; P=0.89). This is consistent with trends observed in the HERA adjuvant trastuzumab trial (12). Lapatinib treatment was only beneficial in those commenced within a year of diagnosis (HR 0.70; 95% CI, 0.50-0.99; P=0.04), with no significant difference between lapatinib and placebo by the pre-specified stratification factors of less than or more than four years post diagnosis. This finding therefore provides evidence for benefit even where Her2 directed therapy is delayed, albeit for a short period. Patients crossing over in the HERA trial after interim results were reported and assignment unblinded received delayed adjuvant trastuzumab and the four year follow up showed that this group had lower rates of relapse than the patients who did not cross over (12). It is recognized that those crossing over may have had different clinical profiles of those who did not. In both of these studies, anti-Her2 therapy was not combined with a taxane, and it is impossible to speculate on whether a similar, or larger, benefit might be obtained by such an approach. Further prospective data may help guide practice in contexts where patients have had extended delays in adjuvant treatment due to complication or comorbidty.

Both the node negative (HR 0.78; 95% CI, 0.57-1.07; P=0.13) and node positive (HR 0.86; 95% CI, 0.69-1.07; P=0.18) groups showed trend toward benefit from lapatinib which was not statistically significant, a result which like the primary endpoint may have been influenced by the intention to treat analysis including 20% of patients not centrally confirmed to be Her2 positive. As the authors rightly comment, high rates of false positive or negatives have significant clinical and economic impact (9). Taking steps to improve the accuracy of Her2 testing may be an efficient strategy for low to middle resource centres in improving early breast cancer outcomes.

**The rapidly evolving landscape of adjuvant Her2 targeted treatment**

The optimal adjuvant treatment for early Her2 positive breast cancer is far from resolved. A number of studies are in progress or recently presented examining new agents and different durations of trastuzumab therapy. Publication of the BCIRG006 study, and ongoing trials of Trastuzumab emtansine (T-DM1) in early breast cancer will necessitate a re-evaluation of roles of anthracycline and taxane chemotherapy which have in recent years formed the backbone of adjuvant chemotherapy in both Her2 positive and Her2 negative breast cancer. The question of duration of Her2 directed therapy is an ongoing one.

**Novel Her2 targeting agents**

Studies are underway in the adjuvant and neo-adjuvant settings of novel combinations of Her2 targeting therapy. Pertuzumab, a monoclonal antibody binding to domain II of Her2 preventing dimerization of Her2-Her3, improves rates of pathologic complete response in combination with neoadjuvant chemotherapy and trastuzumab (13), and the combination of pertuzumab and trastuzumab without cytotoxic chemotherapy produced a pathologic complete response rate of 18%. An adjuvant trial is underway (14). TDM-1 is a novel antibody-cytotoxic drug conjugate that significantly improves progression free survival in metastatic Her2 positive breast cancer compared to capecitabine and lapatinib (9.6 vs. 6.4 mo. HR 0.65; 95% CI, 0.549-0.771; P<0.0001), and median overall survival (30.9 vs. 25.1 months; hazard ratio for death from any cause, 0.68; 95% CI, 0.55 to 0.85; P<0.001) (15). Frequency of grade 3 or more toxicity...
was 13% for thrombocytopenia, diarrhea 20%, PPE 12%, vomiting 4% and elevated liver enzymes approx. 5%. Rates of grade 3 or higher toxicity was lower for TDM-1 than for capecitaine and lapatinib (41% vs. 57%). A single-arm open-label study is underway to assess the safety, feasibility and efficacy of 12 months T-DM1 after anthracycline-based adjuvant/neoadjuvant chemotherapy in patients with early Her2-positive breast cancer (16). A formulation of trastuzumab for subcutaneous administration has been developed and compared to standard intravenous trastuzumab in a phase I/III non-inferiority study with co-primary endpoints of serum trough concentration and pCR. Non-inferiority was concluded with the difference between groups in pCR was 4.7% (95% CI, –4.0% to 13.4%) (17).

Thus, the optimal duration of Her2 targeted therapy has been the focus of several studies, as it is vital to establish not only maximal efficacy but also limit excessive toxicity and cost. A nine week trastuzumab regimen, in combination with either taxane or vinorelbin after anthracycline containing combination, improved survival compared to chemotherapy alone (18) and is a cost effective strategy on health economic modeling. This strategy was adopted by few first world countries (namely New Zealand) but anecdotally is used in resource poor countries to justify abbreviated courses of trastuzumab on economic grounds. Recently, data was presented for six months versus twelve months adjuvant trastuzumab, which failed to meet non-inferiority criteria, although the lower limit of the confidence interval did cross the non-inferiority boundary (19). Conversely, there is no additional benefit for twenty four months of trastuzumab, and twelve remains the standard (20).

The findings of the pre-specified subgroup analyses of Goss et al. (9) highlight a number of questions for further investigation regarding the optimal combinations of Her2 directed therapy, biomarker identification of subgroups for whom there is a differential benefit of such strategies, and even identification of a group for whom cytotoxic chemotherapy may be avoided altogether. The node negative, T1a and T1b tumours may be appropriate candidates for these studies. Several trials have now demonstrated the inferior efficacy and toxicity profile of lapatinib when compared to trastuzumab in the neo-adjuvant and adjuvant settings. Even in the small subset of eligible women for whom intravenous trastuzumab may be considered unaffordable, inaccessible or intolerable, the advantages of lapatinib seem uncertain by these criteria, given the well established toxicity profile and evidence for some benefit of a nine week trastuzumab strategy. It appears single agent lapatinib after chemotherapy, while superior to placebo, will have limited applicability in the current milieu of widely available trastuzumab, the promise of newer Her2 targeting agents, emerging evidence for dual monoclonal antibody combinations, with and without chemotherapy, and alternative trastuzumab formulations. Future investigation should focus on prognostic indicators and biomarkers of responsiveness to determine a more personalized risk benefit profile for combination therapy.

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References


