HER2 status and breast cancer therapy: recent advances
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Abstract
The phenotype imparted by expression of the HER2 gene in breast cancer and progress made in modifying the disease’s natural history through pharmacologically modulating its function has served as a paradigm for rationally targeted therapy and personalized medicine. About 20–25% of breast cancer cases are associated with HER2 gene amplification and overexpression, creating a distinct subtype of breast cancer that is associated with more aggressive behaviour, higher likelihood of overall and brain metastases, and differential responsiveness to certain hormonal and chemotherapeutic agents. Anti-HER2 monoclonal antibodies have led to significant improvements in survival for both advanced and early stage HER2+ breast cancer, while newer agents, including other antibodies and HER2 receptor tyrosine kinase inhibitors and signal transduction modulators, are also demonstrating clinical activity and represent further opportunities to improve curability and quality of life.

Introduction and context
Upon the recognition of the importance of HER2 amplification and overexpression in the outcome of patients with early stage breast cancer, laboratory experiments using anti-HER2 antibodies consistently showed growth inhibitory effects, presumably due to modulation of downstream signal transduction, but also potentially due to activation of the immune system against HER2 epitopes [1,2]. Phase I and II trials showed that a humanized HER2 antibody, trastuzumab (trade name Herceptin®), given as a single agent could lead to transient - but in some cases, long-lived - responses in 15% of advanced breast cancer patients in the second line setting and 26% of patients as first line therapy [3–5]. A pivotal randomized trial showed that the addition of trastuzumab to standard first line chemotherapy in HER2+ advanced breast cancer can improve response rates and time to disease progression (TTP) and also improved median survival by a relative amount of 24%, or an absolute median gain of 5 months, leading to the approval of this drug in HER2+ metastatic breast cancer (Figure 1) [6]. Systemic therapy used in the early stage adjuvant setting has the potential to improve long-term curability, so the logical extension of these findings was to compare the addition of trastuzumab to standard chemotherapy in patients with HER2+ early stage breast cancer, using 1 year of trastuzumab therapy - a length of time that was arbitrary, but at least supported by safety data. Careful cardiac screening and monitoring was incorporated into all four major pivotal trials done worldwide. The two North American trials [N9831 and National Surgical Bowel and Breast Program (NSABP) B-31] used a standard regimen of doxorubicin and cyclophosphamide (AC) for four cycles every 3 weeks followed by paclitaxel either every 3 weeks for four cycles or at a lower dose every week for 12 weeks with or without trastuzumab. Trastuzumab was given with paclitaxel at standard doses. The N9831 trial contained a third arm in which trastuzumab was given following paclitaxel. The Breast Cancer International Research Group (BCIRG) 006 trial used a control arm of AC followed by four cycles of docetaxel. The second arm was administered trastuzumab with docetaxel. A third arm used docetaxel and
carboplatin every 3 weeks for six cycles with trastuzumab concurrently; this arm was based on preclinical synergy noted in preclinical models with both these chemotherapeutic agents and trastuzumab and was also testing whether less cardiotoxicity might be observed with a non-anthracycline arm. The HERA 3-arm study was more permissive and allowed any pre- or postoperative chemotherapy regimen of more than four cycles compared to chemotherapy with either 1 or 2 years of trastuzumab.

All these trials were stopped early or reported at early interim analysis as the effect size was greater than expected, with hazard ratios for recurrence-free survival ranging from 0.48 to 0.67, and absolute differences in disease-free survival at 3–4 years ranging from 5 to 12.8% [7–10]. Significant differences in overall survival were also seen in all trials, and other findings of these pivotal trials are shown on Table 1. Symptomatic cardiac toxicity was seen in 0.4–3.8% of patients, with higher rates seen with concurrent chemotherapy that included an anthracycline, and recovery was seen in most cases [8–11]. Higher age, lower pre-trastuzumab cardiac ejection fraction and history of hypertension or use of anti-hypertensive medications were noted as risk factors for cardiac events, and most, but not all, patients recovered from these side effects [11,12]. Based on these data, trastuzumab has been approved with the regimens used in the North American and BCIRG 006 trials for node-positive and high risk node-negative HER2+ breast cancer.

**Recent advances**

Currently, the use of trastuzumab is considered standard therapy in the first line setting for advanced HER2+ breast cancer, typically in combination with chemotherapy, but is also used as a single agent as initial or second line therapy. There is some controversy about therapy after progression on trastuzumab—the combination of lapatinib and capecitabine is approved on the basis of a randomized trial showing that this combination led to a significant prolongation of TTP [13]. However, trastuzumab plus capecitabine has also been found to prolong TTP compared to capecitabine alone in patients who had progression on trastuzumab-based therapy [14]. In the adjuvant setting, individualized decision-making that balances benefits against risks, particularly cardiomyopathy, is warranted and generally this is indicated in node-positive or high risk node-negative disease, although other tumour and patient factors (tumour grade, age, co-morbidities) all play a role. Only combinations with chemotherapy have been tested in early stage disease, so the optimal chemotherapy partner remains to be defined—in the US, anthracycline and taxane regimens are more commonly used.

### Table 1. Pivotal HER2-targeting adjuvant trials using trastuzumab

<table>
<thead>
<tr>
<th>Trial/experimental regimen</th>
<th>n</th>
<th>Median f/u (years)</th>
<th>HR DFS</th>
<th>HR OS</th>
<th>Absolute % difference DFS</th>
<th>Absolute % difference OS</th>
<th>CHF (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31/N9831: AC→TH</td>
<td>3,968</td>
<td>2.9</td>
<td>0.48</td>
<td>0.65</td>
<td>12.8 at 4 years</td>
<td>3.2 at 4 years</td>
<td>2.5–3.8</td>
<td>[6,7,10]</td>
</tr>
<tr>
<td>HERA: multiple→H</td>
<td>3,401</td>
<td>2</td>
<td>0.64</td>
<td>0.66</td>
<td>6.3 at 3 years</td>
<td>2.7 at 3 years</td>
<td>0.6</td>
<td>[8]</td>
</tr>
<tr>
<td>BCIRG 006: AC→DH</td>
<td>3,222</td>
<td>2</td>
<td>0.61</td>
<td>0.58</td>
<td>6 at 3 years</td>
<td>4 at 3 years</td>
<td>1.9</td>
<td>[9]</td>
</tr>
<tr>
<td>BCIRG 006: DCaH</td>
<td>3,222</td>
<td>2</td>
<td>0.67</td>
<td>0.66</td>
<td>5 at 3 years</td>
<td>2 at 3 years</td>
<td>0.4</td>
<td>[9]</td>
</tr>
</tbody>
</table>

A, doxorubicin; Absolute % difference DFS, absolute percentage difference in disease-free survival; Absolute % difference OS, absolute percentage difference in overall survival; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; Ca, carboplatin; CHF, congestive heart failure (symptomatic); D, docetaxel; H, trastuzumab (Herceptin); HERA, Herceptin Adjuvant; HR DFS, hazard ratio disease-free survival; HR OS, hazard ratio overall survival; Median f/u, median follow-up; n, number of patients; NSABP, National Surgical Adjuvant Breast and Bowel Project; T, paclitaxel.
trastuzumab alone or in combination with hormonal therapy alone has not been tested in randomized trials. Durations of less than 1 year have not been fully tested, although an underpowered Finnish study, known as the FinHer trial, showed efficacy when trastuzumab was used in combination with chemotherapy for a short period [15]. Therapy should be temporarily suspended or permanently discontinued for any clinical cardiac complications, and in some cases for subclinical decrease in ejection fraction.

Newer HER2-targeted agents such as small molecule kinase inhibitors are being tested, with lapatinib now being tested both in advanced and early stage disease, and HKI-272 in early phase trials for HER2+ advanced breast cancer [16]. Pertuzumab, a new antibody that inhibits dimerisation of HER2 with other HER family members, has also shown activity in trastuzumab-refractory disease [17], as has trastuzumab-DMA1, an immunotoxin [18,19]. Combining trastuzumab with HSP90 inhibitors, which affect the trafficking and proper folding of several proteins involved in signal transduction, has also yielded responses in trastuzumab-refractory cases [20].

Implications for clinical practice
The HER2 oncogene represents an important mediator of breast carcinogenesis and is a clinically relevant biomarker. Targeting HER2 with the antibody trastuzumab has been shown to improve outcome in both advanced and early stage disease and represents a standard of care that requires HER analysis of all breast cancer cases. Guidelines for HER2 interpretation and the need to use high-volume and accredited laboratories are critical [21]. Estimations of the risk of recurrence along with hazard reductions from clinical trials need to be juxtaposed against cardiac and other side effects for optimal individualized decision-making. In the advanced setting, newer HER2-targeting agents will be tested more systematically as salvage therapy, and then in first line use with the hopes that more activity, or less toxicity, might be seen. It is not clear if it is best to use a combination of HER2-directed therapies at the outset, or to wait until there is evidence of clinical resistance. Well designed tissue correlative studies may provide newer biomarkers to predict responses to specific HER2-targeted drugs and aid in decision-making as well as in identifying new targets that could be addressed pharmacologically to reverse resistance to trastuzumab or improve outcomes when added to trastuzumab.

Abbreviations
AC, doxorubicin and cyclophosphamide; BCIRG, Breast Cancer International Research Group; NSABP, National Surgical Bowel and Breast Program; TTP, time to disease progression.

Competing interests
The author declares that he has no competing interests.

References

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