Anti-Tumour Treatment

HER2-targeted therapy in breast cancer: A systematic review of neoadjuvant trials

Susan Dent¹, Basak Oyan², Arnd Honig³, Max Mano⁴, Sacha Howell e,*

¹The Ottawa Hospital Cancer Centre, Division of Medical Oncology, Department of Medicine, The University of Ottawa, 501 Smyth Road, Box 912, Ottawa, Ontario, Canada
²Medical Oncology Section, Yeditepe University Hospital, Devletyolu, Ankara Cad 102-104, Istanbul, Kozyatagi 34752, Turkey
³University of Wuerzburg, Josef-Schneider Str. 4, 97080 Wuerzburg, Germany
⁴Instituto do Câncer do Estado de São Paulo, University of São Paulo, Av. Dr. Arnaldo, 251 Cerqueira César, São Paulo/SP, Brazil
⁵The University of Manchester, Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester M20 4BX, United Kingdom

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Targeting human epidermal growth factor receptor 2 (HER2) during or in sequence with chemotherapy improves overall survival in metastatic and early HER2-overexpressing breast cancer. In this paper we systematically review neoadjuvant clinical trial data in HER2-positive breast cancer and discuss key unanswered clinical questions.

All trials of HER2-targeted neoadjuvant therapy were identified through non-date-limited searches of PubMed® and Biosis® and congress abstract book searches from 2000–2011. Eligible trials were prospective, had at least 10 patients and a clear definition of pathological complete response (pCR) rate.

A total of 50 trials fulfilled the eligibility criteria; 41 single-arm phase II studies were identified, 37 with trastuzumab and 4 with lapatinib, with significant variability in baseline tumour characteristics and pCR rates (range 12–66.7%). Of 9 randomised phase II/III trials, 4 assessed the addition of trastuzumab to chemotherapy and a further 5 randomised trials assessed different HER2-targeting approaches. Four of these studies assessed dual HER2-targeting approaches, which universally increased pCR at the expense of increased non-cardiac toxicity when lapatinib, but not pertuzumab, was added to trastuzumab.

Significant advances have been made in HER2 targeting, resulting in a marked increase in the number of breast cancer patients experiencing tumour pCR. Mature data from randomised neoadjuvant and adjuvant studies are awaited for survival outcomes with combination targeted approaches. Unanswered questions centre on the individualisation of therapy and include; which, if any, chemotherapy backbone should be used, and which patients need dual HER2 blockade?

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Introduction

Neoadjuvant therapy in women with early breast cancer improves rates of operability in locally advanced disease and breast conservation in women who would otherwise require a mastectomy.¹² However, meta-analyses of neoadjuvant trials have not shown an improvement in disease-free (DFS) or overall survival (OS) compared to similar treatment delivered after breast surgery.¹² Nevertheless, the neoadjuvant approach offers additional advantages in the assessment of response to both standard therapies and novel agents requiring in vivo validation.

Several classification systems defining the histopathological effects of chemotherapy on breast cancer have been published.³⁷ In clinical trials, pathological complete response (pCR) has been used as a surrogate marker for clinical outcome (including OS) for patients receiving neoadjuvant treatment. Inconsistencies in the definition of pCR have resulted in significant variations reported in the literature.³⁹ The most widely accepted definition of pCR is no residual invasive carcinoma in the breast and axillary lymph nodes. Differences in the definition of pCR hinge on the requirement for clearance of ductal carcinoma in situ in addition to invasive cancer only from the breast, and invasive disease from axillary lymph nodes. Ideally, to aid in the critical evaluation of results, a standardised definition of pCR should be utilised for all clinical trials.
Human epidermal growth factor receptor 2 (HER2) amplification is seen in approximately 20% of breast cancers and is associated with more aggressive disease and worse prognosis.\textsuperscript{10} Trastuzumab, a monoclonal antibody against the extracellular component of the HER2 protein, results in improved DFS and OS in patients with HER2-overexpressing tumours in both the adjuvant and metastatic settings.\textsuperscript{11–13} In the neoadjuvant setting, the achievement of pCR with chemotherapy plus trastuzumab has been shown to correlate well with improved survival outcomes.\textsuperscript{14} More recently, additional HER2-targeted therapies including lapatinib (a tyrosine kinase inhibitor) and pertuzumab (a humanised anti-HER2 monoclonal antibody) have shown promising results in metastatic breast cancer leading to the exploration of dual blockade with a combination of targeted therapies in the neoadjuvant setting.

In this article, we systematically review the literature detailing HER2-targeted approaches in neoadjuvant clinical trials. Pathological complete response rates achieved with a wide range of regimens in phase II and III studies are tabulated and toxicity profiles, particularly in phase III studies, are discussed. Consideration is given to key questions that remain unanswered such as the optimal management of women with residual cancer post-neoadjuvant therapy and strategies to tailor therapy and increase pCR rates.

Methods

Eligible trials were identified through searches of PubMed, Biosis and manual searches of congress abstract books from the American Society of Clinical Oncology (ASCO), San Antonio Breast Cancer Symposium (SABCS), European Cancer Organisation (ECO), European Society for Medical Oncology (ESMO), European Breast Cancer Conference (EBCC) and St. Gallen International Breast Cancer Conference (St. Gallen). No time limit was stipulated for the PubMed searches. Conference proceedings from 2005 to 2011 were searched initially and the search expanded to 2000 to 2005 post hoc.

The PubMed search terms were: [HER2+, or HER-2+, or HER-2-, or HER2-positive, or HER2 positive, or ErB2- positive, or ErB2B positive] AND [trastuzumab, or pertuzumab, or T-DM1, or lapatinib, or neratinib, or HER2-targeted treatment, or anti-HER-2 treatment, or anti-HER2 treatment, or any of the previous terms with ‘therapy’ substituted for ‘treatment’] AND [breast cancer, or breast neoplasm] AND [neoadjuvant, or preoperative, or pre-operative, or primary systemic]. Search limits were set to: clinical trials, randomised trials, meta-analyses, phase II, or phase III.

PubMed was searched for evidence of subsequent publication of conference abstracts using the senior author as the search term. Abstracts without evidence of prospective enrolment of at least 10 patients into a phase II or III trial were excluded, as were studies with no clear definition of pCR unless clarification could be obtained from the conference poster or presentation. If multiple reports on the same dataset were found, only the most recent update was included. Two authors (Sacha Howell and Basak Oyan) reviewed the resulting lists of studies to be included, and consensus was obtained from all authors for disagreements. Pathological complete response rates were transcribed as presented if adequate account was made of all recruited patients in the text of the abstract/publication. Where there was discrepancy, the number recruited was used as the denominator to provide intent-to-treat analysis. In addition to pCR rates, data were collected on tumour size, stage, endocrine receptor status, presence of inflammatory breast cancer, chemotherapy/targeted agent regimen, as well as treatment schedule and duration. ClinicalTrials.gov was also searched for ongoing trials for discussion.

Results

Summary of neoadjuvant trastuzumab studies

The search criteria identified 358 studies although 308 did not meet the eligibility criteria (Fig. 1). Fifty articles met the eligibility criteria and were included in the review. The majority (37 articles) reported on single-arm phase II studies\textsuperscript{15–51} of different chemotherapy backbones with trastuzumab (Supplementary Table 1). A further four single-arm phase II trials examining the role of single HER2 blockade with lapatinib in patients with hormone receptor-positive, or ERbB2 positive, or HER2-positive, or HER-2 positive, or ErbB-2 positive, or HER2+ tumours are summarised in Table 1.\textsuperscript{52–54} Four randomised trials evaluated the role of single-agent trastuzumab added to a chemotherapy backbone versus the same chemotherapy alone (Table 2).\textsuperscript{36–59} A further five randomised trials evaluated the benefit of other HER2 blockade approaches, including four studies on dual-HER2 blockade (Table 3).\textsuperscript{56–64}

Single-arm phase II trastuzumab trials

In the single-arm phase II studies (Supplementary Table 1), which evaluated chemotherapy backbones on a background of single-agent trastuzumab, pCR rates varied widely (range 12–76%)\textsuperscript{15–51} Cross-trial comparison of the relative activity of these regimens has many pitfalls given the variability in disease stage, oestrogen receptor (ER) status, definitions of pCR, as well as the many potential biases inherent to non-randomised studies. Despite these caveats, these trials demonstrated that trastuzumab is active when given in combination with a wide range of different chemotherapy regimens. In addition, they raised important questions for testing in randomised clinical trials, including the role of anthracyclines in sequence or combination with trastuzumab, the optimal taxane partner for trastuzumab, the role of other non-taxane-, non-anthracycline agents and novel targeted therapies.

Single-arm lapatinib trials

Two single-arm studies have explored the combination of lapatinib and trastuzumab (Table 1).\textsuperscript{52,53} Chang et al. treated women with relatively large tumours (median tumour size 6 cm) with 12 weeks of lapatinib and trastuzumab without the addition of chemotherapy.\textsuperscript{52} Women with ER-positive cancers also received letrozole with or without goserelin in order to block ER/HER cross-talk. The overall rate of pCR in the breast was 28%. Despite treatment with endocrine therapy, patients with ER-positive tumours achieved a lower pCR rate (21%) compared to those with ER-negative expression (42%). The omission of chemotherapy was associated with a good toxicity profile.

Callahan et al. presented preliminary safety and efficacy data on the combination of trastuzumab and lapatinib with docetaxel and carboplatin for six q3-weekly cycles.\textsuperscript{54} In the first 21 patients (including six in a dose escalation phase), the pCR rate of 43% was achieved with ‘manageable’ toxicity. In two small trials (involving 30 and 32 patients, respectively), lapatinib was added to a taxane ( Nab-paclitaxel or paclitaxel) chemotherapy backbone with pCR rates of 17.9% and 9.4%, respectively.\textsuperscript{54,55}

Randomised trials of chemotherapy ± trastuzumab

A total of four randomised (phase II and III) clinical trials have investigated the addition of trastuzumab to neoadjuvant chemotherapy (Table 2).\textsuperscript{36–59} Overall, these trials reported an increase in pCR rates with the addition of trastuzumab to chemotherapy (pCR 26–65%), compared to chemotherapy alone (pCR 19–27%). This appears to be relatively independent of the type of chemotherapy employed. In the first of these studies (MDACC), women
were randomised to block sequential taxanes and anthracycline chemotherapy with or without trastuzumab throughout treatment.\(^5^6\) This approach re-explored the concept of concurrent administration of anthracycline and trastuzumab, which had largely been abandoned after high rates of cardiac failure were seen in the metastatic setting.\(^1^1,^5^6\) The pCR rate in the combination arm was 65% compared to only 26% in those receiving chemotherapy alone, resulting in early closure of the study (\(n = 42\)). Safety data were relatively reassuring. The high pCR rates were shown to be reproducible in a small expansion phase of the trial and the regimen was shown to be feasible outside of a clinical trial setting.\(^5^6,^6^5,^6^6\)

In the larger NOAH study (randomised phase III), 235 patients with HER2-positive, locally advanced breast cancer (including HER2 = human epidermal growth factor receptor 2, pCR = complete pathological response (defined as no invasive tumour in breast and axilla, if not otherwise specified), EBC = early breast cancer, DCIS = ductal carcinoma in situ, ST1 = supplementary table 1, T1 = table 1, T3 = table 3.

### Table 1

<table>
<thead>
<tr>
<th>Ref. #</th>
<th>Study name, phase</th>
<th>(\text{N})</th>
<th>Regimen</th>
<th>Neo tx duration, weeks</th>
<th>Stage</th>
<th>HR negative,%</th>
<th>pCR,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>TBCRC 006 RP2 Chang, et al. J Clin Oncol 2011</td>
<td>66</td>
<td>(T + L \pm \text{goserelin}) 12 (Tqwk) + L 1000 mg for 12 weeks If ER+, premenopausal: letrozole If ER+, postmenopausal: letrozole + goserelin</td>
<td>12</td>
<td>&gt;3 cm or &gt;2 cm and (\text{cN}^+)</td>
<td>38</td>
<td>28 (≥1 cm residual invasive tumour in breast)</td>
</tr>
<tr>
<td>53</td>
<td>RP2 Callahan, et al. Cancer Res 2010</td>
<td>20</td>
<td>(T + L \text{ Docetaxel} + T + L) 1 (Tq3wk) + L 1000 mg, 3 wks) (\rightarrow) 6 (Tq3wk) (\rightarrow) 6 (L 1000 mg/d, q3wk) (\rightarrow) 6 (D 75 mg/m(^2) Car AUC: 5-6, q3wk)</td>
<td>21</td>
<td>IIA 40% IIB 35% IIA 10% IIB 15%</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>54</td>
<td>Kaklamani, et al. Breast Cancer Res Treat 2012</td>
<td>30</td>
<td>(\text{Nab-P} + L) 4 (Nab-P 260 mg/m(^2), q3wk) (\rightarrow) (L 1500 mg for 2 weeks) (\rightarrow) L 1500 mg + 12 (P 80 mg/m(^2), qwk)</td>
<td>12</td>
<td>I 13.3% II 63.3% III 23.4% IIB 44% IIC 34% IV 22%</td>
<td>60</td>
<td>17.9</td>
</tr>
<tr>
<td>55</td>
<td>P2 Boussen, et al. J Clin Oncol 2010</td>
<td>32</td>
<td>(L \rightarrow P) L 1500 mg for 2 weeks (\rightarrow) L 1500 mg + 12 (P 80 mg/m(^2), qwk)</td>
<td>14</td>
<td>Not given</td>
<td>9.4%</td>
<td></td>
</tr>
</tbody>
</table>

Ref. \# = reference number, Neo tx = neoadjuvant treatment, HR = hormone receptor, pCR = pathological complete response (defined as no invasive tumour in breast and axilla, if not otherwise specified), RP2 = randomised phase II study, T = trastuzumab, L = lapatinib, Tqwk = 4 mg/kg loading then 2 mg/kg every week, wks = weeks, ER = oestrogen receptor, D = docetaxel, Car = carboplatin, Tq3wk = 8 mg/kg loading then 6 mg/kg every 3 weeks, q3wk = every 3 weeks, AUC = area under the concentration–time curve, Nab-P = nanoparticle albumin-bound paclitaxel, P2 = phase II study, P = paclitaxel, qwk = every week.

* All patients planned for surgery before starting therapy.

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Fig. 1. HER2 = human epidermal growth factor receptor 2, pCR = complete pathological response (defined as no invasive tumour in breast and axilla, if not otherwise specified), EBC = early breast cancer, DCIS = ductal carcinoma in situ, ST1 = supplementary table 1, T1 = table 1, T3 = table 3.
inflammatory breast cancer) were randomised to receive epirubi-
cin/taxane/CMF-based chemotherapy with or without trast-
uzumab, concurrent with all chemotherapy.\(^67\) The primary
epithelial event-free survival (EFS), which was improved with
the addition of trastuzumab (3-year EFS 71% vs. 56%, hazard
ratio 0.59 [95% CI, 0.38 to 0.90]; \(P = 0.013\)), as was the secondary end-
point of pCR rate (total pCR: 38% vs. 19%, \(P = 0.001\); breast pCR:
43% vs. 22%, \(P = 0.0007\)). The investigational arm appeared to be
safe, with no major short term cardiac issues reported. The patients
in the NOAH trial had more advanced disease than those in the
MDACC trial (69%\(^57\) had T4 and/or inflammatory breast cancer
compared with 67%\(^26\) with T2 disease in the MDACC trial), which
may explain the lower pCR rates observed.

In a French randomised phase II trial, 120 patients with stage II
and III HER2-positive breast cancer were randomised to receive
epirubicin/cyclophosphamide followed by docetaxel with or with-
out concurrent trastuzumab.\(^59\) In this trial, pCR rates favoured the
experimental arm (26% vs. 19%), with no major safety issues re-
ported. Similarly, in ABCSG-24, a subgroup of 90 patients with
HER2-positive, locally advanced disease were randomised to receive
epirubicin/docetaxel or epirubicin/docetaxel/capecitabine with or
without trastuzumab, and a statistically non-significant in-
crease in pCR was observed with the addition of trastuzumab (40% vs.
26.7%).\(^59\)

These results have led to the adoption of combination
chemotherapy and trastuzumab as the standard of care in the
neoadjuvant setting for women with HER2-overexpressing non-
metastatic breast cancer.\(^67-69\)

### Strategies to improve on trastuzumab-based therapy

Despite the improved pCR rates seen with the addition of trast-
uzumab to chemotherapy (Table 2), the majority of patients with
breast cancer do not experience a pCR and even if this is achieved it
serves as a small minority still experience relapse.\(^44\) Thus in cancers where
the HER2 pathway is the key driver of cell proliferation and cell
survival, primary and acquired resistance to trastuzumab are key
issues. Some potential mechanisms of resistance and strategies to
overcome them are presented in Table 4. Dual blockade with a
combination of targeted therapies has been explored as an alterna-
tive treatment strategy to overcome resistance. Although several
novel agents targeting HER2 have been developed, the most ma-
data are available for lapatinib and pertuzumab (Table 152–
55 and Table 3.\(^60-64\))

### Randomised trials comparing HER2-targeting approaches

Five randomised neoadjuvant trials that compared HER2-tar-
geted agents individually or in combination were identified (Ta-
ble 3).\(^60-64\) The targeted therapies in each study were combined
with conventional chemotherapy backbones comprising taxanes and/or
anthracyclines. In the open-label NeoALTTO trial, patients received
paclitaxel with lapatinib, trastuzumab, or the combina-
tion.\(^60\) The pCR rate in the breast and axilla with the combination
of lapatinib to anthracycline-/taxane-based chemotherapy, and dem-
strated a significantly superior pCR rate in patients treated with
lapatinib than trastuzumab (32% vs. 1%; \(P = 0.97\)). The combination
overcame dual blockade with a

### Table 2

Randomised trials of chemotherapy ± trastuzumab.

<table>
<thead>
<tr>
<th>Ref. #</th>
<th>Study name, phase, citation</th>
<th>N</th>
<th>Regimen</th>
<th>Neo tx duration, weeks</th>
<th>Stage</th>
<th>HR negative,%</th>
<th>pCR,%</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>MDACC RP3 Buzdar, et al. J Clin Oncol 2005</td>
<td>42</td>
<td>Arm A: P → FEC Arm B: P + T → FEC + T (P 225 mg/m(^2) over 24 h, q3wk) ± 12 (Tqwk) → 4 (FEC 500[d1,4]/75/500 mg/m(^2), q3wk) ± 12 (Tqwk)</td>
<td>24</td>
<td>T1 10%</td>
<td>43</td>
<td>Arm A: 26</td>
</tr>
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<tr>
<td>57</td>
<td>NOAH RP3 Gianni, et al Lancet 2010</td>
<td>235</td>
<td>Arm A: AP → P → CMF Arm B: AP + T → P + T → CMF + T (AP 60/150 mg/m(^2), q3wk) → 3 (P 175 mg/m(^2), q3wk) → 3 (CMF 600/40/600 mg/m(^2) d1,8, q4wk) ± Tq3wk with AP and P, q4wk with CMF</td>
<td>40</td>
<td>T3N1 or T4 or any T N2,3 T4a-c 42.5% IBC = 26.5%</td>
<td>64</td>
<td>Total pCR Arm A: 19%</td>
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</tr>
<tr>
<td>58</td>
<td>RP2 Pierga, et al. Breast Cancer Res Treat 2010</td>
<td>120</td>
<td>Arm A: EC → D Arm B: EC → D + T (EC 75/750 mg/m(^2), q3wk) → 4 (D 100 mg/m(^2), q3wk) + 12 (Tqwk)</td>
<td>24</td>
<td>T2 &gt; 4 cm N0- T2 49%</td>
<td>41</td>
<td>Arm A: 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>59</td>
<td>ABCSG-24 RP3 Steger, et al Cancer Res 2009</td>
<td>90</td>
<td>Arm A: ED + Cap Arm B: ED + Cap + T (ED 75/75 mg/m(^2), q3wk) ± 6 (Cap 1000 mg/m(^2) bid, d1–14, q3wk) ± 6 (Tq3wk)</td>
<td>18</td>
<td>T1 19%</td>
<td>40</td>
<td>Arm A: 26</td>
</tr>
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<td></td>
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</tbody>
</table>

pCR definition not provided.

Ref. # = reference number, Neo tx = neoadjuvant treatment, HR = hormone receptor, pCR = pathological complete response (defined as no invasive tumour in breast and axilla, if not otherwise specified). RP3 = randomised phase III study, P = paclitaxel, FEC = 5-fluorouracil, epirubicin, and cyclophosphamide, T = trastuzumab, q3wk = every 3 weeks, Tqwk = every 4 weeks, IBC = inflammatory breast cancer, RP2 = randomised phase II study, E = epirubicin, C = cyclophosphamide, D = docetaxel, Cap = capecitabine, bid = twice daily.
comprised sequential blocks of taxane then anthracycline-containing chemotherapy. The study of Holmes et al.\textsuperscript{62} reported very high pCR rates in the NeoSphere RP2 study,\textsuperscript{64} which compared the combination of dual HER2 targeting with chemotherapy. The combination of dual HER2 targeting with chemotherapy resulted in a significantly higher pCR rate (39.3%) when compared with the same chemotherapy and single agent trastuzumab (21.5%; \textit{P} = 0.014) or pertuzumab (17.7%; \textit{P} = 0.003). Importantly, the addition of a second, targeted anti-HER2 agent did not increase toxicity significantly. In the adjuvant setting, the combination of pertuzumab and trastuzumab with chemotherapy is being evaluated in the international, multicentre, randomised phase III BIG 4-11 trial (APHINITY; NCT01358877).

The four-arm randomised phase II NeoSphere study\textsuperscript{64} (Table 3) compared the combination of pertuzumab and trastuzumab with or without docetaxel and single-agent trastuzumab or pertuzumab in combination with docetaxel. Treatment was given for a total of 12 weeks prior to surgery and all patients then received additional anthracycline-based chemotherapy postoperatively. The pertuzumab and trastuzumab combination without docetaxel induced pCR in breast and axilla in 11.2% and in breast alone in 16.8% of women. The combination of dual HER2 targeting with chemotherapy resulted in a significantly higher pCR rate (39.3%) when compared with the same chemotherapy and single agent trastuzumab (21.5%; \textit{P} = 0.014) or pertuzumab (17.7%; \textit{P} = 0.003). Importantly, the addition of a second, targeted anti-HER2 agent did not increase toxicity significantly. In the adjuvant setting, the combination of pertuzumab and trastuzumab with chemotherapy is being evaluated in the international, multicentre, randomised phase III BIG 4-11 trial (APHINITY; NCT01358877).

Two further neoadjuvant studies are exploring single-agent versus combination lapatinib and trastuzumab in the neoadjuvant setting on a paclitaxel backbone, either with (NSABP-B41\textsuperscript{76}) or without (CALGB 40601; NCT00770809) preoperative anthracycline prior to commencing HER2-targeted therapy. NSABP-B41 reported initial results after the searches for this article were conducted, and demonstrated high rates of breast and axillary pCR with AC-paclitaxel in combination with either trastuzumab (pCR 52.5%) or

### Table 3
Randomised trials comparing HER2-targeting approaches.

<table>
<thead>
<tr>
<th>Ref. #</th>
<th>Study name, phase, citation</th>
<th>N</th>
<th>Regimen</th>
<th>Neo tx duration, weeks</th>
<th>Stage</th>
<th>HR negative, %</th>
<th>pCR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>NeoALTTO RP3 Baselga, et al. Lancet 2012</td>
<td>455</td>
<td>Arm A: T → T + P</td>
<td>18</td>
<td>&gt;2 cm</td>
<td>49</td>
<td>Arm A: 27.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm A: T → T + P</td>
<td>6 (Tqwk) → 12 (Tqwk) + 12 (P 80 mg/m², qwk)</td>
<td>T2</td>
<td>58%</td>
<td>Arm B: 20.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P 80 mg/m², qwk)</td>
<td>12 (P 80 mg/m², qwk)</td>
<td>T3/4 42%</td>
<td>Arm C: 46.8</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Arm C: T + L → T + L + P</td>
<td>12 (P 80 mg/m², qwk)</td>
<td>T3</td>
<td>53%</td>
<td>Arm C: 46.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm C: T + L → T + L + P</td>
<td>12 (P 80 mg/m², qwk)</td>
<td>T4</td>
<td>58%</td>
<td>Arm C: 46.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm A: EC + T → D + T</td>
<td>4 (EC 90/600 mg/m², q3wk) + 12 (Tqwk) + 4 (D 100 mg/m², q3wk) + 4 (Tq3wk)</td>
<td>T3/4a-d or T3/4 74%</td>
<td>Arm A: 30.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm B: EC + L → D + L</td>
<td>4 (EC 90/600 mg/m², q3wk) + (L 1000–1250 mg/d × 12 weeks) → 4 (D 100 mg/m², q3wk) + (L 1000–1250 mg/d × 12 weeks)</td>
<td>T2</td>
<td>5%</td>
<td>Arm B: 30.3</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Arm C: EC + P + L</td>
<td>24</td>
<td>12</td>
<td>22.7</td>
<td>Arm B: 30.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm A: T → FEC + T → P + T</td>
<td>2 (Tqwk) → 4 (FEC 500/75/500 mg/m², q3wk) + 12 (Tqwk)</td>
<td>IIA</td>
<td>25</td>
<td>Arm A: 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm A: T → FEC + T → P + T</td>
<td>12 (P 80 mg/m², qwk) + (L 1250 mg/d × 12 weeks) → 4 (FEC 500/75/500 mg/m², q3wk) + (L 1250 mg/d × 12 weeks) → 12 (P 80 mg/m², qwk) + (L 1250 mg/d × 12 weeks)</td>
<td>IIA 18%</td>
<td>Arm A: 25</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Arm A: C + T + P + L</td>
<td>4 (D 75–100 mg/m², q3wk) + 4 (Tq3wk) + 4 (Pert 840 mg/m², q3wk) + 4 (Pert 840 mg/m², q3wk)</td>
<td>IIA 18%</td>
<td>Arm A: 25</td>
<td></td>
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<td></td>
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<td></td>
<td>Arm A: D + T + P + Pert</td>
<td>4 (D 75–100 mg/m², q3wk) + 4 (Tq3wk) + 4 (Pert 840 → 420 mg/m², q3wk) + 4 (Pert 840 → 420 mg/m², q3wk)</td>
<td>IIA</td>
<td>21.5</td>
<td>Arm A: 21.5</td>
</tr>
</tbody>
</table>

\textit{pCR definition not provided.}  
\textit{Ref. # = reference number, Neo tx = neoadjuvant treatment, HR = hormone receptor, pCR = pathological complete response (defined as no invasive tumour in breast and axilla, if not otherwise specified), RP3 = randomised phase III study, T = trastuzumab, P = paclitaxel, Tqwk = 4 mg/kg loading then 2 mg/kg every week, qwk = every week, L = lapatinib, wk = week, E = epirubicin, C = cyclophosphamide, D = docetaxel, q3wk = every 3 weeks, Tqwk = 8 mg/kg loading then 6 mg/kg every 3 weeks, IBC = inflammatory breast cancer, FEC = fluorouracil, epirubicin, and cyclophosphamide, RP2 = randomised phase II study, Pert = pertuzumab, LABC = locally advanced breast cancer.}
lapatinib (pCR 53.2%).70 There was no statistically significant difference in pCR rate with chemotherapy and trastuzumab alone vs. the combination of lapatinib and trastuzumab (52.5% vs. 62% P = 0.095).

**Targeted agents and toxicity**

**Cardiac toxicity**

Cardiac toxicity was the predominant adverse effect identified with trastuzumab in the metastatic breast cancer clinical trials (CHF 27%11,12). However, unlike the irreversible, dose-dependent apoptosis and necrosis of cardiomyocytes induced by anthracyclines,71 trastuzumab induced cardiac toxicity appears to be largely reversible. Similarly, the effects of lapatinib on the myocardium appear largely reversible, not cumulative or dose related, and ultrastructural myocardial changes are not generally seen.72 Pertuzumab has been generally well tolerated by patients enrolled in ongoing clinical trials, with a low incidence of cardiac dysfunction.73 The potential clinical benefit of concurrent administration of anthracyclines and trastuzumab has been re-explored in the neoadjuvant setting in several randomised studies with no apparent detrimental impact on cardiac health. One should remain cautious however when considering adoption of this approach outside of the clinical trial setting, given the small numbers of highly selected patients enrolled in these studies and the short duration of follow-up.29,56,59,61–64

Cardiotoxicity in trials of dual HER2 inhibition – trastuzumab with lapatinib or pertuzumab

In the NeoALLTO study (Table 3), patients received anthracycline-based chemotherapy postoperatively with concurrent administration of lapatinib, or trastuzumab, or both. No major cardiac dysfunction has been reported to date.60 Similarly in GeparQuinto, the concurrent administration of trastuzumab or lapatinib with epirubicin/cyclophosphamide-docetaxel resulted in low levels of symptomatic cardiotoxicity (1%).61 In the NeoSphere study, the addition of pertuzumab to trastuzumab resulted in only one reported case of congestive heart failure in a woman with a history of coronary stents and cardiac treatment with digitalis for an unrelated cardiac problem.64 Changes in left ventricular ejection fraction were within 15% in all of the trastuzumab, pertuzumab, and combination groups, suggesting that the addition of pertuzumab over a short course of four cycles of chemotherapy did not add significantly to short term cardiotoxicity.64 These results are encouraging; however, we await the longer term safety data, in particular from the adjuvant portion of this trial in which anthracyclines were delivered with concurrent trastuzumab following surgery.

Most recently, the TRYPHAENA study73 tested the addition of pertuzumab and trastuzumab to both anthracycline and taxane portions of neoadjuvant chemotherapy or to the taxane portion only. The primary endpoint of the study was cardiac safety. The results showed no increase in cardiotoxicity when targeted treatment was delivered with the anthracycline portion concurrently. Similarly, low levels of short-term cardiotoxicity were seen in this study with six cycles of non-anthracycline chemotherapy and trastuzumab plus pertuzumab.

To date, the limited data available on dual targeted therapies does not suggest an increase in cardiac toxicity. This is reflected in the change in the trastuzumab label to include its use in the neoadjuvant setting in combination with chemotherapy. However, the duration of follow-up has been relatively short and as such, the widespread adoption of concurrent anthracyclines with trastuzumab in a ‘real world’ setting is premature. Bozovic-Spasojevic et al.74 undertook a combined analysis of 3 neoadjuvant trials75,56,57 in which anthracyclines were combined with trastuzumab. The concurrent use of anthracycline-based chemotherapy and trastuzumab was associated with a trend towards an increased risk of cardiac toxicity (OR 1.95, 95% CI 1.16–3.29; P = 0.036), thus highlighting the need for extra vigilance when considering the adoption of this treatment approach in the non-clinical trial setting.

**Non-cardiac toxicity with HER2-targeted therapies**

While most attention has focused on the potential cardiac toxicity of HER2-targeted therapies, several significant non-cardiac toxicities have been observed in phase II/III clinical trials. In NeoALLTO, women randomised to the lapatinib-containing arms experienced significant grade 3/4 diarrhoea (21% lapatinib; 23%...
lapatinib/trastuzumab.60 Similar rates of diarrhoea have been reported in smaller phase II neoadjuvant trials,54,63 necessitating extra vigilance in toxicity monitoring and supportive care measures. In the run-in portion of the GeparQuinto trial,61 82% of the 60 patients enrolled in the lapatinib arm experienced grade 3/4 neutropenia necessitating the mandatory administration of growth factors for patients randomised to lapatinib and docetaxel in the main study. In addition, 34.5% of patients in the run-in phase discontinued treatment early, leading to a reduction in the dose of lapatinib from 1250 mg/day to 1000 mg/day in the main study.

In NeoSphere, the addition of pertuzumab to trastuzumab in combination with docetaxel did not significantly increase toxicity.64 There were numerically more cases of grade 3/4 asthenia (2% vs. 0%) in the triple therapy arm but the incidence of grade 3/4 neutropenia was lower (45% vs. 57%). The incidence of febrile neutropenia (7% vs. 8%) as well as grade 3/4 diarrhoea (6% vs. 4%) was similar in both arms. In contrast, the addition of pertuzumab to trastuzumab and docetaxel in the metastatic setting resulted in significantly more grade 3/4 diarrhoea (7.9% vs. 5.0%),75 possibly reflecting the longer duration of exposure in this trial. In NeoSphere, the combination of pertuzumab plus trastuzumab without docetaxel was very well tolerated, with only 7% of patients experiencing any grade 3/4 toxicity, confirming that the majority of side effects of combination therapy are due to the cytotoxic agents.64

It is imperative that we continue to prospectively collect information on the toxicities of these targeted therapies not only in the clinical trial setting but also in clinical practice. Longer follow-up of targeted therapy trials, particularly in those patients treated with curative intent, are needed to establish the long-term safety of these agents.

Novel HER2-targeted agents in ongoing neoadjuvant clinical trials

Neratinib

Neratinib, similar to lapatinib, is an oral, dual–activity but irreversible pan-inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinases. It targets EGFR, HER2, and HER4,76 and is an active agent in patients whose disease has progressed following trastuzumab-based therapy.77 A randomised phase II study (NSABP FB-7) of neratinib versus trastuzumab in combination with weekly paclitaxel, followed by doxorubicin and cyclophosphamide as neoadjuvant therapy is currently recruiting women with HER2-positive, locally advanced breast cancer (NCT01008150). Neratinib is also one of several investigational agents to be tested in the neoadjuvant I-SPY 2 trial on a backbone of paclitaxel followed by doxorubicin/cyclophosphamide (NCT01042379).

Trastuzumab–emtansine (T-DM1)

T-DM1 is a novel agent, comprised of trastuzumab, a stable linker, and emtansine, a potent microtubule inhibitor.78,79 Upon binding to HER2, T-DM1 is internalised and emtansine is released intracellularly, causing direct cytotoxicity,80 thus T-DM1 requires only HER2 expression for activity not a functional HER2 signalling pathway. A phase II trial evaluating the safety and efficacy of T-DM1 in the neoadjuvant/adijuvant setting after the completion of anthracycline-based chemotherapy in patients with early HER2-positive breast cancer has completed accrual (NCT01196052) and a neoadjuvant comparison of T-DM1 versus trastuzumab in combination with endocrine therapy is actively recruiting (NCT01745965).

Afinitin (BIBW 2992)

Afinitin is a potent, irreversible receptor tyrosine kinase inhibitor targeting HER1 and HER2. The drug has been tested in a small, three-arm neoadjuvant study as a single-agent compared with lapatinib or trastuzumab (each given for 6 weeks prior to definitive breast surgery) and results are pending (NCT00826267). A second single arm study, currently recruiting is assessing the efficacy and safety of afatinib in combination with trastuzumab and paclitaxel prior to an anthracycline and trastuzumab combination and breast surgery (NCT01594177).

Discussion

The addition of HER2-targeted agents to a chemotherapy backbone in the neoadjuvant setting, has resulted in improved pCR rates (26–65%) over the same chemotherapy partner alone (19–28%) in women with HER2-amplified breast cancers.56–59 However, a number of women treated with this approach (single HER2 blockade/chemotherapy) will not achieve a pCR and it is in this population that dual HER2 blockade may be beneficial. Several trials have demonstrated the clinical benefit of dual HER2 blockade in addition to a chemotherapy backbone.60,62–64 Mature data from these and ongoing adjuvant trials such as ALTTO (NCT00490139) and APHINITY (NCT01358877) are needed to establish the value of dual HER2 blockade on DFS and OS. In addition, the feasibility of dual HER2 blockade in the non-clinical trial setting is dependent on the toxicity profile of these combinations as discussed previously.

A number of clinical trials have tested the combination of anthracyclines given concurrently with anti-HER2 therapy, a practise largely abandoned due to high rates of cardiac toxicity observed with this approach in the metastatic setting. None of these trials have shown significant increase in short-term cardiac toxicity and the trastuzumab label has recently been changed by the European Medicines Agency (EMA)60 to include treatment ‘in combination with neoadjuvant chemotherapy’, which could contain an anthracycline. However, no study has yet shown a significant improvement in pCR rate or any survival endpoint with the addition of a HER2-targeted agent to both the anthracycline and taxane portion of a regimen versus the taxane portion alone, or indeed to taxane-based chemotherapy plus a HER2-targeted agent in the absence of an anthracycline. Indeed in TRYPHAENA73 the pCR rates and incidence of short-term cardiotoxicity were comparable in all three arms. Until the time that such outcome data, and indeed longer term cardiotoxicity data are available, regimes that employ concurrent anthracycline and HER2-targeted agents should be reserved for patients who fulfil the strict entry criteria and monitoring requirements of the studies in which these regimes were tested.

The optimal duration of neoadjuvant therapy is not clear. Although six to eight cycles of chemotherapy prior to surgery is established practise, the impressive pCR rate with only 12 weeks of dual HER2-targeted agents plus chemotherapy in the NeoSphere64 and NeoALTTO65 studies suggest that shorter durations of highly active regimes may be feasible. As all patients had treatment postoperatively to balance out the chemotherapy regimes in these trials, future studies will be required to determine the optimal duration of neoadjuvant therapy. The optimal duration of trastuzumab therapy has not been established. Current guidelines suggest that completion of 1 year of HER2-targeted therapy is considered standard.67,68 Shorter durations may be similarly efficacious81 but further trials are underway to test this hypothesis such as SOLID (NCT00593697), PERSEPHONE (NCT00712140), and PHARE (NCT00381901). Preliminary results from PHARE, designed to test 6 months vs. 12 months of adjuvant trastuzumab using a non-inferiority design, were recently presented.82 The conclusion was that 6 months of treatment could not be classed as non-inferior to 12 months statistically. Retrospective sub-group analysis suggested that the 6-month regimen may be inferior in women.
with ER-negative disease who received sequential chemotherapy then trastuzumab, although this did not reach statistical significance.

Perhaps the greatest challenge in breast oncology is the personalisation of therapy through identification of predictive biomarkers of tumour sensitivity. In the neoadjuvant setting, dynamic changes in biomarkers can also be assessed either through serial tumour biopsy, blood draw for circulating tumour cells (CTCs) and other markers or molecular imaging to assess tumour metabolic pathways or drug distribution. All of these approaches are currently under investigation in neoadjuvant trials of HER2-targeted agents. Although it is beyond the scope of this paper to review all such data, some examples merit special mention. In the study of Holmes et al. all patients had core needle biopsies at baseline and 2 weeks into HER2-targeted therapy. Results were analysed based on the subsequent achievement of pCR in the breast and demonstrated that resistant tumours were significantly more likely to have intact PI3K, autophagy and stem cell proliferation pathways. Differences between treatment arms (trastuzumab vs. lapatinib vs. combination) were also detected although patient numbers were small and these results will require verification in the translational studies of larger trials such as NeoALTO, GeparQuinto and NeoSphere.

Translational results from the GeparQuinto study have already been published for circulating biomarkers. In particular, a decrease in levels early after therapy initiation was predictive of response to lapatinib-based but not trastuzumab-based treatment. CTCs may also be useful biomarkers of prognosis and response to therapy, however they are only detectable in a minority of patients undergoing neoadjuvant therapy, limiting their clinical utility with current detection methods. Intriguingly, in the GeparQuattro neoadjuvant study, of the 22% (46/213) of patients with > 1 CTC/7.5 mL sample, HER2-overexpressing CTCs were found in 8 patients with HER2-negative primary tumours. Similarly, CTCs scored HER2-negative or weakly HER2-positive before or after neoadjuvant therapy in 11 of 21 patients with HER2-positive primary tumours, potentially identifying a mechanism of trastuzumab resistance. There was no correlation between CTC levels and pCR in this or the NeoALTO study, in which a similar low percentage of patients had detectable CTCs.

The neoadjuvant setting provides an ideal testing ground for agents, where relatively small trials, with carefully conducted sequential biopsy and correlative biomarker studies, are taking us closer to the goal of personalised medicine. Perhaps the best example of this is the I-SPY 2 Trial (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2; NCT01042379), which seeks to identify improved treatment regimens for subsets of patients on the basis of molecular characteristics (biomarker signatures) of their disease. The trial design is adaptive such that regimens that show a high Bayesian predictive probability of being more effective than standard therapy will graduate from the trial with their corresponding biomarker signature(s) and regimens will be dropped if they show a low probability of improved efficacy. Imaging in the I-SPY 2 trial is with sequential biopsy and correlative biomarker studies, are taking us closer to the goal of personalised medicine.

Conclusions

Overall, the future is looking brighter for patients diagnosed with HER2-positive breast cancer with combinations of HER2-targeted agents showing great promise in improving outcomes. The neoadjuvant setting provides an ideal testing ground for novel agents, where relatively small trials, with carefully conducted sequential biopsy and correlative biomarker studies, are taking us closer to the goal of personalised medicine.

Conflict of interest statement

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Author contributions

Literature search: Sacha Howell and Basak Oyan Conception and design: All authors. Collection and assembly of data: All authors. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctrv.2013.01.002.
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