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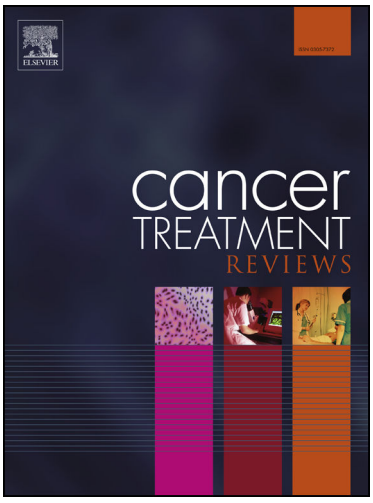

Anti-tumour Treatment

Risk-based decision-making in the treatment of HER2-positive early breast cancer: Recommendations based on the current state of knowledge

Christian Jackisch, Patricia Cortazar, Charles E. Geyer Jr, Luca Gianni, Joseph Gligorov, Zuzana Machackova, Edith A. Perez, Andreas Schneeweiss, Sara M. Tolaney, Michael Untch, Andrew Wardley, Martine Piccart

PII: S0305-7372(21)00077-3
DOI: https://doi.org/10.1016/j.ctrv.2021.102229
Reference: YCTRV 102229

To appear in: *Cancer Treatment Reviews Cancer Treatment Reviews*

Received Date: 11 March 2021
Revised Date: 14 May 2021
Accepted Date: 17 May 2021

Please cite this article as: Jackisch, C., Cortazar, P., Geyer Jr, C.E., Gianni, L., Gligorov, J., Zuzana Machackova, Perez, E.A., Schneeweiss, A., Tolaney, S.M., Untch, M., Wardley, A., Piccart, M., Risk-based decision-making in the treatment of HER2-positive early breast cancer: Recommendations based on the current state of knowledge, *Cancer Treatment Reviews Cancer Treatment Reviews* (2021), doi: https://doi.org/10.1016/j.ctrv.2021.102229

Risk-based decision-making in the treatment of HER2-positive early breast cancer: Recommendations based on the current state of knowledge

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Role of the funding source

This article was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Employees of the sponsor were involved in the writing and reviewing of the review; and in the decision to submit the article for publication in conjunction with the academic authors.

Article type

Review article

Word count

5335; limit is 5000 words (excluding references, tables, figures)

Figures/tables

4/6

Highlights

- Risk of relapse must be evaluated to optimise treatment for HER2-positive early breast cancer.
- Decision about whether to offer neoadjuvant chemotherapy plus pertuzumab–trastuzumab.
- Patients with a pathological complete response continue HER2-targeted therapy to complete 18 cycles (before and after surgery).
- Patients with residual disease after standard-of-care neoadjuvant chemotherapy plus HER2-targeted therapy should receive post-neoadjuvant trastuzumab emtansine to complete 14 cycles (after surgery).
- For patients who undergo surgery first, treatment with adjuvant chemotherapy plus pertuzumab–trastuzumab is the standard of care for those patients with a higher risk of relapse.
- For patients with node-negative disease and tumours <2cm at presentation, paclitaxel for 12 weeks plus 18 cycles of trastuzumab might be a good option for the post-operative adjuvant therapy.

References

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Abstract (238/250 words)

Treatment of HER2-positive early breast cancer (EBC) continues to evolve with neoadjuvant (pre-operative) and adjuvant (post-operative) HER2-targeted therapies as standard-of-care. There are two important decision points. The first involves deciding between neoadjuvant therapy or proceeding directly to surgery. Neoadjuvant chemotherapy (NACT) plus pertuzumab–trastuzumab is appropriate for

patients with high-risk HER2-positive EBC (tumour diameter ≥2cm, and/or node-positive disease). Patients with node-negative disease and tumour diameter <2cm are candidates for upfront surgery followed by paclitaxel for 12 weeks plus 18 cycles of trastuzumab, with the option to add pertuzumab (if pN+). The second decision point involves the pathohistological result at surgery after neoadjuvant therapy. Total pathological complete response (tpCR: ypT0/is, ypN0) is associated with improved survival endpoints. Patients with tumours ≥2cm and/or node-positive disease at diagnosis who have a tpCR after dual blockade should continue pertuzumab–trastuzumab in the adjuvant setting to complete 1 year (18 cycles) of treatment. For patients with invasive residual disease, 14 cycles of post-neoadjuvant trastuzumab emtansine (T-DM1) therapy significantly increases invasive-DFS compared with trastuzumab. Extended adjuvant therapy with neratinib is an option in selected patients (HER2-positive and oestrogen receptor [ER]-positive) who have completed adjuvant trastuzumab-based therapy. Less aggressive chemotherapy regimens are recommended in populations with a lower risk of recurrence (patients with small tumours without axillary involvement; patients unlikely to tolerate anthracycline-taxane or taxane-carboplatin regimens). Ultimately, treatment recommendations should be consistent with local and international guidelines. Further studies will guide optimisation of treatment for patients with HER2-positive EBC according to the risk of disease recurrence.

Keywords (6): HER2-postive early breast cancer; pertuzumab; trastuzumab; T-DM1, neoadjuvant therapy; neratinib.

Introduction

The HER2-positive early breast cancer (EBC) treatment landscape evolved steadily over two decades [1]. Pivotal adjuvant trials [2-6] transformed standards-of-care, catalysing transition from chemotherapy to chemotherapy-plus-trastuzumab (significantly improving disease-free/overall survival [DFS/OS]). Neoadjuvant treatment opened two major avenues: increased pathological complete response (pCR; therefore, increased DFS and potentially OS) [7], and a new therapy selection window: “post-neoadjuvant treatment [8-14].” Recently, post-neoadjuvant trastuzumab emtansine (T-DM1) was evaluated for invasive residual disease at surgery after neoadjuvant chemotherapy (NACT) plus anti-HER2 therapy [14]. Extended adjuvant neratinib has been evaluated post-adjuvant trastuzumab [15,16]. Chemotherapy de-escalation with trastuzumab has been evaluated in selected subgroups with low relapse risk (mainly phase II trials), to reduce toxicity without compromising outcomes [17-19]. However, there is no clinical consensus for such strategies; optimal treatment is still standard-of-care chemotherapy plus anti-HER2 therapy.

We discuss evolving clinical risk-based decision-making approaches for HER2-targeted therapy; integrating recent data including those generated by clinical trials.

Methods

Journal publications (last 5 years) and congress abstracts (last 2 years: ASCO/ESMO/SABCS/EBCC/St. Gallen) were reviewed.

Journal publications were identified by a PubMed search of English language publications over a 5-year period (June 2013–June 2018) using the following search terms:

“HER2-positive” OR “ERBB2-positive” OR “neu-positive” AND (“early breast cancer” OR “localised breast cancer” OR “localized breast cancer”) AND

1. (”trastuzumab” OR “pertuzumab” OR “anti-HER2 treatment” OR “anti-HER2 therapy”);
2. (“optimisation” OR “optimization” OR “optimal” OR “dose reduction” OR “escalation” OR “timing” OR “risk”).

Results were screened manually to identify clinical trials (identified through the title or abstract stating clinical trial and/or phase I, II, II or IV number, or having a clinicaltrials.gov or EUDRACT identifier code in the abstract).

Discussion

Clinical risk-based decision-making

In the changing paradigm, initial treatment selection should be underpinned by assessing recurrence risk by multidisciplinary teams at diagnosis to define an optimal treatment pathway that encompasses neoadjuvant, adjuvant (including post-neoadjuvant) or extended adjuvant therapy >1 year.

To optimise treatment selection, we need to identify subgroups at increased relapse risk that would benefit from dual blockade, and subgroups at relatively low risk, in which chemotherapy may be de-escalated. Defining risk involves evaluating tumour stage and clinical nodal status, patient-related (comorbidity/histology/tumour

type/tumour grade/proliferation) and biological characteristics (HER2/hormone receptor [HR] status), which all affect therapy choice and influence response.

The treatment algorithm continues to evolve (Figure 1). Patients with low recurrence risk are currently defined as having small (<2cm diameter), node-negative tumours; patients with higher risk, with tumours ≥2cm and/or node-positive disease [20-23]. There are two important clinical-trial supported decision points for managing patients at high risk. 1) To initiate neoadjuvant systemic therapy or primary surgery. Patients with ≥2cm tumours or node-positive disease at presentation (by palpation, sonography or biopsy) should be treated with standard NACT plus dual HER2 blockade (pertuzumab–trastuzumab). 2) Presence/absence of invasive residual disease after NACT plus anti-HER2 therapy treatment; patients with residual invasive cancer after standard neoadjuvant therapy should receive T-DM1 for 14 cycles. Evidence suggests that those with pCR should continue HER2-targeted therapy to complete 1 year (18 cycles) with pertuzumab–trastuzumab [20-23]. Some uncertainty remains in cases of pCR for patients with node-negative disease and ≥2cm tumours at diagnosis; post-neoadjuvant trastuzumab may be sufficient [22]. However, if the initial risk was such that the use of NACT plus dual blockade was justified, achieving pCR while receiving pertuzumab plus trastuzumab should not trigger treatment de-escalation to trastuzumab alone.

Trastuzumab: the core adjuvant therapy component

Trastuzumab, a recombinant HER2-targeting humanised monoclonal antibody, inhibits HER2 signalling (inhibiting proliferation), triggers antibody-dependent cellular cytotoxicity and may contribute to adaptive immunity development [1,24,25]. Several

landmark studies demonstrated its inclusion in adjuvant regimens significantly improved outcomes versus chemotherapy-only [2-6]. Long-term follow-up confirmed that improvements were durable, leading to significant OS improvements regardless of chemotherapy partner (± anthracyclines) [26-28]. Meta-analyses showed the benefit extended to women with tumours ≤2cm in diameter ± axillary involvement [29]. In early trials, trastuzumab was typically administered for 1 year [26].

Dual anti-HER2 therapy

The next step in adjuvant therapy's evolution was adding a second anti-HER2 therapy with trastuzumab-complementary activity. Pertuzumab, a HER2 dimerisation domain-directed monoclonal antibody, inhibits ligand-initiated intracellular signalling through MAP kinase and PI3K [30]. Lapatinib [31], neratinib [32] and tucatinib [33] are tyrosine kinase inhibitors (TKIs) that inhibit HER2's intracellular TK domains [1].

In ALTTO [34], patients with HER2-positive EBC were randomised to 1 years' trastuzumab, lapatinib, or trastuzumab plus lapatinib, or 12–18 weeks' trastuzumab then 28–34 weeks' lapatinib concurrent/sequential with chemotherapy per physician's choice. The lapatinib-alone arm was terminated early for futility. The remaining comparisons showed, although there were fewer events in the dual therapy arms, neither concurrent trastuzumab plus lapatinib nor sequential trastuzumab→lapatinib produced pre-specified statistically significant improvements in DFS versus trastuzumab. Adding lapatinib was also associated with more adverse events (AEs; Grade 3/4 diarrhoea/rash/hepatotoxicity) [34].

Based on NeoSphere, adjuvant pertuzumab–trastuzumab was evaluated in APHINITY (**Table 1**) [12]. Patients with node-positive or high-risk (tumour diameter >1cm) node-negative operable BC who had not received neoadjuvant therapy were eligible. Patients with node-negative tumours 0.5–1.0cm with high risk features (histologic/nuclear Grade 3/HR-negative/<35 years) were initially eligible; enrolment of patients with node-negative disease was subsequently capped. Patients were randomised to receive, with standard chemotherapy, 1 years' pertuzumab–trastuzumab or placebo–trastuzumab. Pertuzumab–trastuzumab and chemotherapy significantly improved 3-year invasive DFS (IDFS; primary endpoint) versus placebo (hazard ratio [HRa] 0.81; 95% CI 0.66–1.00; p=0.045), reducing relative recurrence risk by 19% [12]. The effect was driven by patients at higher relapse risk due to lymph-node involvement/HR-negative disease. Safety was consistent with previous studies, there were no new safety issues noted, but low-grade diarrhoea was more common in the pertuzumab group than the placebo group.

The 6-year update was recently reported [35]. Between-arm IDFS differences remained consistent, with a 24% relative reduction in recurrence risk after 6 years' median follow-up (HRa 0.76; 95% CI 0.64–0.91). In node-positive disease, 6-year IDFS was 87.9% with pertuzumab–trastuzumab and 83.4% with placebo–trastuzumab (absolute difference 4.5%; HRa 0.72; 95% CI 0.59–0.87). Adding pertuzumab had no statistically significant effect in node-negative disease (HRa 1.02; 95% CI 0.69–1.53). With longer follow-up, pertuzumab's effect was apparent regardless of HR status. In HR-positive disease, pertuzumab–trastuzumab was associated with better 6-year IDFS than placebo–trastuzumab (HRa 0.73; 95% CI 0.59–0.92), whereas in HR-negative disease the between-group difference non-

significantly favoured pertuzumab–trastuzumab (HRa 0.83; 95% CI 0.63–1.10). There were fewer deaths in the pertuzumab–trastuzumab arm (125 [5.2%] versus 147 [6.1%]), although OS differences were non-significant (HRa 0.85; 95% CI 0.67–1.07, p=0.170). However, data remain immature (43% of events required for final analysis). Follow-up is ongoing; final OS will be assessed at 640 events. No new cardiac concerns emerged.

Based on the APHINITY 6-year data, the ESMO Magnitude of Clinical Benefit Score (ESMO-MCBS) for adjuvant pertuzumab–trastuzumab in HER2-positive EBC has recently been upgraded to an 'A', which is the highest score possible for a regimen in the curative setting.[36]

Anti-HER2 adjuvant therapy duration

Standard adjuvant anti-HER2 therapy lasts 1 year (18 q3w cycles), including patients who start in the neoadjuvant setting [20-23]. HERA compared safety and efficacy of 1 and 2 years' trastuzumab; 2 years did not provide additional benefits [2,26]. Other trials examined shorter durations [37-40]. Recent meta-analyses demonstrated that 1 year remains optimal [41,42]. However, PERSEPHONE [43] demonstrated non-inferiority of 0.5 versus 1 years' adjuvant trastuzumab for DFS (89.4% [6 months]; 89.8% [1 year]; non-inferiority margin 3%; HRa 1.07; 90% CI 0.93–1.24) and OS (93.8% and 94.8%; 1.14; 0.95–1.37) [43]. Subgroups in which 1 year might be superior included ER-negative disease (HRa 1.26; 95% CI 0.96–1.65), patients who received: taxane without an anthracycline (2.46; 1.27–4.77), NACT (1.50; 1.03–2.17) and trastuzumab concurrently with chemotherapy (1.45; 1.10–1.92). Further work is required to identify subgroups potentially suited to an abbreviated regimen. Thus, 1 year remains standard-of-care [20-23].

Extending adjuvant therapy with TKIs

Although 2 years' adjuvant trastuzumab proved no more effective than 1 in HERA [26], ExteNET demonstrated that a longer duration could be effective by changing to a TKI. ExteNET investigated one additional year of neratinib after standard neoadjuvant and adjuvant chemotherapy plus trastuzumab [11,16]. This resulted in improved 5-year DFS versus placebo (HRa 0.73; 95% CI 0.57–0.92). Subgroup analyses showed only patients with HR-positive disease receiving concurrent endocrine therapy (ET) benefitted from neratinib (IDFS HRa 0.60; 95% CI 0.43–0.83 versus 0.95; 0.66–1.35 in HR-negative disease). Benefits appeared greater in patients who started neratinib ≤1 year post-trastuzumab completion (HRa 0.70; 95% CI 0.54–0.90) versus >1 year post-completion (1.00; 0.51–1.94). Benefits came at the cost of more AEs, particularly diarrhoea; however, no long-term effects from neratinib-associated diarrhoea were observed. During neratinib treatment, 55% experienced Grade 1/2 and 40% experienced Grade 3 diarrhoea without prophylaxis; much higher than reported with prophylaxis subsequently [44].

Neoadjuvant therapy

Neoadjuvant therapy is standard-of-care for most patients with high-risk disease [45]. Originally used to render tumours operable/to avoid mastectomy, NACT did not improve long-term outcomes versus adjuvant chemotherapy in patients with operable disease [46]. Today, it provides a better understanding of disease biology and is useful in tailoring treatment. It is integral to multidisciplinary treatment; pCR status provides additional important prognostic information at the patient level that reflects tumour biology. With pCR, a treatment can be continued in the post-

neoadjuvant setting, whereas with residual disease, the plan may be modified to improve outcomes [20-23].

Neoadjuvant pertuzumab–trastuzumab

Neoadjuvant pertuzumab–trastuzumab with chemotherapy [8,10] significantly improves pCR versus single anti-HER2 therapy plus chemotherapy, and is widely considered standard-of-care. NeoSphere demonstrated breast pCR superiority of pertuzumab–trastuzumab plus docetaxel versus other combinations of anti-HER2 therapies ± docetaxel [8]. All patients received 3 adjuvant 5-fluorouracil/epirubicin/cyclophosphamide (FEC) cycles post-surgery and those receiving antibodies alone also received adjuvant docetaxel. NeoSphere was not powered to demonstrate progression-free survival (PFS; equivalent to EFS as noted by the authors) significance; 5-year rates were 86% (pertuzumab–trastuzumab plus docetaxel), 81% (trastuzumab plus docetaxel) and 73% (pertuzumab plus docetaxel or pertuzumab–trastuzumab) [47].

The cardiac safety TRYPHAENA study demonstrated low overall rates of symptomatic left ventricular (LV) systolic dysfunction with total pCR (tpCR; ypT0/is, ypN0) rates of 54.7–63.6% with pertuzumab–trastuzumab plus anthracycline-containing and non-anthracycline containing regimens [10].

From NACT to post-neoadjuvant therapy: Individualising therapy on the basis of outcome

The landmark pooled analysis (CTNeoBC) of ~12,000 patients with neoadjuvant treatment demonstrated pCR after NACT was associated with improved outcomes

[7], i.e., significantly better event-free survival (HRa 0.48; 95% CI 0.43–0.54) and OS (0.36; 0.31–0.42). It should be noted that CTNeoBC included patients from the full BC spectrum; pCR–outcome association was strongest for triple-negative and HER2-positive BC [7].

A recently completed pooled analysis confirmed pCR (ypT0/is, ypN0)–long-term outcome associations [48]. 3,710 patients were included; 1,499 achieved pCR (median follow-up: 61 months). Results demonstrate that baseline tumour size and nodal status (traditional poor-prognostic factors), remain important even post-pCR [48].

A pooled analysis of 1,764 patients who received trastuzumab, pertuzumab, or both as part of a systemic neoadjuvant regimen showed that pCR-attaining patients had better long-term outcomes than those with residual disease, regardless of HR status/clinical stage. However, it is important to be aware that some pCR-achieving patients still experienced recurrence; therefore, the best possible therapy should be continued after surgery and further efforts should be made to define prognostic factors for recurrence [49].

Post-neoadjuvant therapy to optimise outcomes in women with residual disease

Given that patients with residual disease post-neoadjuvant therapy have worse prognosis, strategies are needed to optimise therapy. KATHERINE was designed to address this unmet need by optimising anti-HER2 therapy and evaluating the potential for adapting treatment post-neoadjuvant therapy. KATHERINE enrolled

patients with residual invasive disease at surgery after completing ≥6 cycles (16 weeks) of chemotherapy containing ≥9 weeks' taxane-based therapy and 9 weeks' trastuzumab. Anthracyclines, alkylating agents and a second anti-HER2 agent were permitted. Patients were randomised to 14 cycles of T-DM1 or trastuzumab [14]. ~18% per arm previously received pertuzumab plus trastuzumab. After ~41 months' median follow-up, T-DM1 significantly improved IDFS versus trastuzumab (HRa 0.50; 95% CI 0.39–0.64; p<0.001). Three-year IDFS improved 11.3% by switching to T-DM1. Benefits were apparent in all subgroups regardless of extent of residual disease, including those with node-negative disease and residual tumours <1cm [50].

Safety was consistent with the known T-DM1 safety profile, including liver enzyme elevations and thrombocytopenia. T-DM1-treated patients experienced more AEs than trastuzumab-treated. Discontinuation rates due to AEs were higher with T-DM1 (18.0% versus 2.1%) as were serious AEs (12.7% versus 8.1%) [14].

Exploratory analyses have examined the extent of T-DM1 benefit in subgroups. IDFS benefit was consistent regardless of HR status and previous anti-HER2 therapy [14]. Comparing pre-neoadjuvant tumour and surgical samples showed evidence of a change from HER2-positive to HER2-negative in 70/845 patients. Among these, no IDFS events occurred in those randomised to T-DM1 versus 11 in those randomised to trastuzumab [51]. Based on these findings, it is not currently recommended to re-examine HR and/or HER2 status in the breast and/or axilla in cases of residual disease, as systemic therapy choice is based on HR and HER2 status at presentation. Exploratory analyses of surgical tissue samples indicated that *PIK3CA*

status did not influence outcomes. High versus low *HER2* gene expression was associated with worse IDFS with trastuzumab, but not T-DM1 [52].

T-DM1 reduced incidence of distant recurrence as a first event (10.5% versus 15.9%) with trastuzumab (HRa 0.60; 95% CI, 0.45–0.79) [14]. A subset of these patients experienced central nervous system (CNS) recurrence as a first event: 5.9% randomised to T-DM1; 4.3%, to trastuzumab [14]. In patients who only had CNS recurrence, time to detection of CNS metastases was longer with T-DM1 (17.5 months) versus trastuzumab (11.9 months) [53]. Results suggest that T-DM1 provides good control of visceral disease while highlighting an unmet medical need for effective post-neoadjuvant treatment to prevent recurrence in the CNS.

KATHERINE established a new standard-of-care for patients with residual disease post-neoadjuvant therapy [20-23]. It must be emphasised that the only way to identify patients who benefit from post-neoadjuvant T-DM-1 is through routine neoadjuvant therapy use.

De-escalation of NACT

De-escalation studies are shown in **Table 2**.

KRISTINE assessed de-escalation in patients with stage II/III BC to determine whether tolerability could be improved without compromising efficacy by forgoing conventional chemotherapy [54]. Patients were randomised to neoadjuvant T-DM1 plus pertuzumab or chemotherapy (docetaxel and carboplatin) plus pertuzumab–trastuzumab q3w for six cycles. Patients continued treatment with T-DM1 plus

pertuzumab or pertuzumab–trastuzumab after surgery, respectively, to complete 18 cycles (1 year). At primary analysis, the T-DM1-based regimen produced significantly lower tpCR (ypT0/is, ypN0) than conventional chemotherapy (44.4% versus 55.7%, p=0.016) [54]. After 3 years' follow-up, EFS event risk was higher with T-DM1 plus pertuzumab (HRa 2.61; 95% CI 1.36–4.98), driven by locoregional progression events pre-surgery (15 versus 0) and more non-invasive recurrence events post-surgery (3 versus 0) [55]. IDFS event risk post-surgery was similar between arms (HRa 1.11; 95% CI 0.52–2.40]). However, as IDFS does not capture events prior to surgery (including locoregional progressions observed in 6.7% of patients in the T-DM1 plus pertuzumab arm) and event rates were low overall, IDFS data should be interpreted with caution. The T-DM1-based regimen had a favourable safety profile overall. Patients receiving neoadjuvant T-DM1 plus pertuzumab had fewer Grade ≥3 AEs and serious AEs versus conventional chemotherapy plus pertuzumab–trastuzumab [54]. During adjuvant treatment Grade ≥3 AEs and AEs leading to treatment discontinuation were more common in the T-DM1 plus pertuzumab arm. In summary, KRISTINE did not meet its primary endpoint of improved pCR with the T-DM1-based regimen; consequently, these data did not change the standard-of-care neoadjuvant treatment.

WSG-TP-II evaluated chemotherapy de-escalation in patients with HR-positive/HER2-positive EBC [56]. Patients received 12 weeks' ET (tamoxifen/aromatase inhibitor)/paclitaxel plus pertuzumab–trastuzumab. Adjuvant chemotherapy omission was allowed in patients achieving pCR after 12 weeks. Pertuzumab–trastuzumab was continued post-surgery to complete 1 year. pCR (ypT0/is, ypN0) was achieved in 24% in the ET arm and 57% in the paclitaxel arm.

Survival results are awaited. This strategy is, at present, hypothesis-generating and may be the basis for further evaluation.

WSG-ADAPT used predictive information from early response to de-escalate therapy [19]. It enrolled patients with HER2-negative or HER2-positive disease; the latter received HER2-targeted therapy. Patients with HER2-positive and HR-positive EBC received 12 weeks' neoadjuvant T-DM1 ± ET, or trastuzumab with ET. tpCR (ypT0, ypN0) was similar in patients who received T-DM1 (41.0%) and T-DM1 plus ET (41.5%); both were higher than trastuzumab with ET (15.1%). Early response was defined as proliferation decrease ≥30% of Ki-67 from baseline or low cellularity (<500 invasive tumour cells) in a biopsy obtained at 3 weeks. tpCR was significantly higher in early responders (35.7%, 71/199) than non-responders (19.8%, 20/101) (odds ratio 2.2; 95% CI 1.24–4.19, p=0.005). AEs were higher with T-DM1 (most common: fatigue, nausea, headache, elevations in ALT and AST, and thrombocytopenia); although there were relatively few therapy-related severe AEs (5.3 versus. 3.1% with trastuzumab) [19]. Importantly, there was no alopecia, peripheral polyneuropathy or febrile neutropenia reported.

Long-term efficacy results were recently reported and showed no differences in DFS/OS despite higher pCR rates [57]; likely due to standard chemotherapy, which was administered to all patients with residual disease and most with pCR. 5-year DFS results in patients who achieved pCR after 12 weeks of T-DM1 ± ET or without further chemotherapy may allow prospective de-escalation trials in certain patients. These strategies should be evaluated in a phase III randomised controlled trial, to further assess the promising effect summarized here.

De-escalation of NACT using biomarkers

Several studies used Ki-67 to identify patients suitable for de-escalation, with mixed results. In PerELISA, postmenopausal women with HER2-positive, HR-positive EBC received letrozole for 2 weeks, then underwent biopsy for Ki-67 re-evaluation. Patients with responses (>20% Ki-67 reduction from baseline) continued letrozole and received five pertuzumab–trastuzumab cycles [58]. Non-responders received paclitaxel plus pertuzumab–trastuzumab. tpCR (ypT0/is, ypN0) was achieved in 9/44 responders (20.5%) and 13/16 non-responders (81.3%). Results suggest that Ki-67 may identify a subset of patients with HR-positive disease who might achieve tpCR without chemotherapy, and alternatively, that lack of response might identify patients who may derive a particular benefit from neoadjuvant paclitaxel plus trastuzumab-pertuzumab [58]. Larger studies must be performed before reaching definite conclusions.

Patients with HER2-positive/HR-negative EBC in WSG-ADAPT received 12 weeks' pertuzumab–trastuzumab ± paclitaxel. tpCR (ypT0/is ypN0) was higher with pertuzumab–trastuzumab plus paclitaxel (90.5%) versus pertuzumab–trastuzumab (34.4%) [59]. In the pertuzumab–trastuzumab arm (N=92), 38, 30 and 24 patients were classified as responders, unclassifiable or non-responders, respectively; pCR rates were 44.7%, 42.9% and 8.3%. Thus, although failing to show non-inferiority of the chemotherapy-free and chemotherapy-containing regimens, WSG-ADAPT showed that change in proliferation correlates with pCR [59].

PerELISA and WSG-ADAPT suggest that biomarkers like Ki-67 could provide useful information for tailoring treatment beyond “tumour burden” alone, and possibly reduce exposure to ineffective therapies in patients unlikely to achieve pCR. However, the clinical utility of proliferation markers obtained 3 weeks after initiating treatment is questionable given a significant proportion of patients were unclassifiable in WSG-ADAPT. Nonetheless, early biomarkers should continue to be pursued, perhaps combined with functional imaging.

In a collaborative translational research effort, a set of four “baseline” biomarkers were found to be correlated with probability of achieving pCR with a chemotherapy-free regimen of trastuzumab and lapatinib. These included a PAM50 HER2-enriched subtype, strong IHC expression of HER2 (≧97.5% IHC 3+), lack of *PIK3CA* mutations and a *HER2* FISH ratio of ≥4.6 [60]. Whether this multiparameter classifier would also apply to dual blockade with pertuzumab–trastuzumab remains to be seen.

In any event, more emphasis on RNA-based biomarkers such as the PAM50 subclassification is warranted, as they may indicate varying degrees of HER2 “oncogene addiction” [61].

Evidence for the use of tumour-infiltrating lymphocytes (TILs) as predictive and prognostic biomarkers for response to therapy in HER2-positive EBC is conflicting; further data from prospectively planned analyses of treatment response by TILs levels is needed.[62,63]

A strong correlation was observed between early changes in tumour standardised uptake values corrected for lean body mass (SULmax) on FDG-PET and tpCR (ypT0/is, ypN0) after 4 cycles of neoadjuvant pertuzumab–trastuzumab for stage II/III HER2-positive ER-negative BC in TBCRC026 (median reduction in SULmax for

tpCR versus no pCR: 63.8% versus 33.5%, p<0.001) [64]. A major challenge with generalised Ki-67 use is lack of concordance among pathologists; thus, further work in this important area will be very relevant.

PHERGain also uses FDG-PET as a biomarker to tailor neoadjuvant therapy (NCT03161353). Patients are randomised to NACT plus pertuzumab–trastuzumab (A) or pertuzumab–trastuzumab ± ET (B); adapted by FDG-PET outcome after two cycles (responders continue regimen B, non-responders switch to regimen A). All patients will receive 18 pertuzumab–trastuzumab cycles. pCR (ypT0/is, N0) was achieved in 57.7% of patients in group A and 35.4% in group B (37.9% of PET-responders, i.e. without any chemotherapy, and 25.9% of PET-non-responders after chemotherapy plus pertuzumab–trastuzumab) [17]. Proportions of patients with AEs, serious AEs and a ≥10% decline in global health status was greater in group A versus B. Group B responders without pCR will receive chemotherapy post-surgery. Follow-up is ongoing to determine 3-year IDFS.

Adjuvant chemotherapy de-escalation

Less aggressive chemotherapy regimens are recommended in lower-risk populations, e.g., patients with smaller tumours without axillary involvement or frail patients less likely to tolerate anthracyclines-taxanes/taxanes-carboplatin.

APT is a phase II trial that evaluated adjuvant chemotherapy de-escalation in patients with small, node-negative HER2-positive tumours (T≤3cm) (**Table 3**) [65]. Treatment comprised 12 weeks' paclitaxel plus 18 trastuzumab cycles. Primary endpoint was DFS. In 3–7-year follow-up analyses, patients were at minimal risk of

recurrence and distant recurrence (98.7% survival without invasive disease at 3 years [65]; 93% DFS at 7 years [66]). Among 410 patients, 23 DFS events occurred during 6.5 years' follow-up; only four were distant recurrences. Most patients had HR-positive disease (67%). Based on these data, patients at lower risk of relapse (T1 tumours, no axillary involvement) are considered candidates for paclitaxel-trastuzumab as standard adjuvant therapy.

ATEMPT investigated efficacy of 1 year of adjuvant T-DM1 and whether T-DM1 was associated with less toxicity than paclitaxel-trastuzumab [67]. Patients with stage I HER2-positive EBC were allocated to receive 17 T-DM1 cycles q3w, or qw paclitaxel plus trastuzumab for 12 weeks followed by trastuzumab q3w for 39 weeks (**Table 3**). Co-primary endpoints were DFS in the T-DM1 arm (pre-defined acceptable threshold at 3 years), and differences in clinically relevant toxicity (CRT) rates between the arms. After 3.1 years' median follow-up, DFS was 97.7% (95% CI 96.2%–99.3%) in the TDM1 arm; in-line with the threshold [67]. However, longer follow-up is desirable, as relapses can occur beyond 3 years, particularly in a patient population enriched with the HER2-positive/HR-positive subtype.

CRT incidence was the same in both arms (46%; p=0.91). Despite not meeting the prespecified difference criterion, there were important differences between the safety profiles. Thrombocytopenia and elevated ALT and bilirubin were more common with T-DM1 versus paclitaxel-trastuzumab. Additionally, 17% of T-DM1 patients discontinued therapy early due to AEs. However, serially collected patient-reported outcomes indicated that these patients had better QoL and better work productivity versus those receiving paclitaxel-trastuzumab [68]. Cost differential and the lack of

regulatory approval for T-DM1 in this setting should also be considered for this decision.

Replacing adjuvant taxanes and trastuzumab with TDM-1 in high-risk patients

KAITLIN evaluated replacing taxanes and trastuzumab with T-DM1 in adjuvant regimens for patients with high-risk disease; indicated by node-positive disease or node-negative, HR-negative disease and tumours >2cm [69]. Patients were randomly allocated within 9 weeks of surgery to 3 or 4 anthracycline-based chemotherapy cycles followed by T-DM1 plus pertuzumab or pertuzumab–trastuzumab plus a taxane. KAITLIN did not meet one of the co-primary endpoints: 3-year IDFS in the ITT population was similar between groups (93.1% versus 94.2%, respectively; HRa 0.98; 95% CI 0.72–1.32). Grade ≥3 AE (51.8% versus 55.4%) and SAE (21.4% versus 23.3%) rates were similar, but more patients discontinued T-DM1 (26.8%) than trastuzumab (4.0%). T-DM1-pertuzumab does not provide an efficacy advantage over pertuzumab–trastuzumab plus taxane-based adjuvant therapy in patients with high-risk EBC [69].

Tailoring treatment regimens to minimise cardiotoxicity risks

This remains at the forefront of adjuvant and neoadjuvant therapy goals. Cardiotoxicity is a significant adverse effect associated with conventional chemotherapy (particularly high-dose anthracyclines) and HER2-targeted therapy, where much of the data are from adjuvant trials. Trastuzumab-related cardiac dysfunction does not appear to be dose-dependent and is often manageable and reversible. Long-term follow-up shows that most cardiac events occur on-treatment, with few additional events occurring post-anti-HER2 treatment [70,71]. Baseline risk

factors associated with cardiac event development in key trials included baseline LVEF <60%, hypertension, body mass index >25, age ≥60 and non-Caucasian ethnicity [70]. SAFE-HEaRt showed that HER2-targeted therapy can be administered to patients with reduced LVEF (40–49%) under close monitoring while receiving cardioprotective medications [72].

To date, anthracycline plus taxane-based chemotherapy is the most used NACT regimen across subtypes [73]. However, an anthracycline-free regimen (docetaxel and carboplatin) plus 1 years' trastuzumab was associated with less congestive heart failure (CHF) and cardiac dysfunction compared with an anthracycline-containing regimen (doxorubicin and cyclophosphamide followed by docetaxel, AC-T) plus 1 years' trastuzumab in BCIRG006 [5]. CHF incidence was 0.7% with AC-T, 2.0% with AC-T plus trastuzumab, and 0.4% with docetaxel/carboplatin plus trastuzumab. Proportions of patients with >10% reductions in LVEF were 11.2%, 18.6% and 9.4%, respectively [5].

Five-year DFS rates were 84% with the anthracycline-containing and 81% with the anthracycline-free regimen at the cost of more CHF episodes [5]. There was no difference in OS. For this reason the anthracycline-free regimen is recommended for patients at higher cardiotoxicity risk [74].

It is important to note that cardiotoxicity observed in trials after the initial pivotal trials is reassuring even in those with anthracycline use (ALTTO [34], APHINITY [12]), with rates of cardiac events being lower that in initially reported HER2 adjuvant trials.

TRAIN-2 showed that some patients do well without anthracyclines [18,75]. Patients were randomised to nine neoadjuvant paclitaxel/carboplatin cycles or three of FEC followed by six of paclitaxel/carboplatin. All received concurrent pertuzumab–trastuzumab. 68% achieved pCR (ypT0/is, ypN0) with the anthracycline-free regimen (67% in the anthracycline-containing regimen); 3-year EFS rates were 93.5% and 92.7%, respectively; and 3-year OS rates were 98.2% and 97.7%. Although these outcome numbers appear very similar, the trial was not designed or powered to demonstrate non-inferiority of the non-anthracycline regimen, as shown by the broad 95% confidence interval of the EFS hazard ratios (Table 2).

Significant decreases in LV function occurred in 3% in the anthracycline-free and 8% in the anthracycline-containing arm. New malignancies occurred more often following anthracycline-containing than anthracycline-free treatment (5% versus 2%). Potential long-term impacts of these findings on clinical symptomatology requires further evaluation [75].

Subcutaneous pertuzumab–trastuzumab

Trastuzumab is available in a subcutaneous formulation, co-formulated with recombinant human hyaluronidase. Subcutaneous administration is preferred by patients over intravenous [76-78], with no difference in 6-year EFS/OS [79]. A fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection has recently been approved by the FDA and EMA, and provides non-inferior serum trough concentrations and nearly identical tpCR rates to separate intravenous infusions [80]. Patients prefer subcutaneous over IV administration (85% versus 14%) [81]. Recently completed trials [82,83] show that subcutaneous trastuzumab home administration is feasible and preferred by patients. An expanded access

study (NCT04395508) is evaluating the safety of home-administered subcutaneous pertuzumab–trastuzumab by home health nurses. A sub-study of a planned chemotherapy de-escalation trial (DECRESCENDO; NCT04675827) will include secondary evaluation of the fixed-dose combination in patients with EBC that allows for treatment outside oncology centres.

Future perspectives

Much progress has been made in optimising treatment, but many avenues remain open to exploration. There is a need to better match patients with available therapies based on individual characteristics, including biomarkers. This can be achieved by generating new trial evidence and examining long-term outcomes in pre-existing studies to optimise biomarker use (tumour-infiltrating lymphocytes, subtyping of immune cells, early response as measured by PET-FDG, circulating tumour DNA). Although biomarker work over the last 15 years has only yielded prognostic factors, it is hoped further work will identify biomarkers that can identify patients with early response and, alternatively, early recurrence. Patients with HER2-enriched subtypes have higher pCR rates after neoadjuvant therapy, including anti-HER2 agents, after accounting for HR status and chemotherapy [84]. It remains to be determined whether therapy can be de-escalated using this marker; further dedicated clinical trials are needed in this area.

The HER2DX-combined prognostic score, developed using clinical–pathological data on TILs, PAM50 subtypes and expression of 55 genes in a retrospective analysis of the Short-HER phase III trial, has been used to identify patients with HER2-positive

EBC who may be candidates for escalated or de-escalated systemic treatment [85]. Further clinical validation of this tool is needed.

There is a need to understand better the significance of biomarker status alteration. Tumour heterogeneity occurs with respect to HR and HER2 status [61,86-88]. Re-evaluation of biomarkers in patients with residual disease is of interest to researchers; there are no guidelines on how to manage patients with altered tumour biomarker status [89]. An association between HER2 heterogeneity and pCR rate for patients with HER2-positive EBC treated with neoadjuvant TDM-1 plus pertuzumab has been described; however, this has not yet been validated for clinical use [90].

Future clinical trials should be designed to further optimise therapy in patients on the basis of pCR. In patients who achieve pCR after 12–16 weeks of pertuzumab–trastuzumab plus a taxane, it remains to be determined whether anthracycline chemotherapy can be avoided, at least in some subsets. CompassHER2-pCR (NCT04266249), HER2-RADiCAL (clinicaltrials.gov pending) and DECRESCENDO will enrol patients who have been given neoadjuvant taxane plus trastuzumab-pertuzumab (no anthracycline).

Combining cancer immunotherapies and chemotherapy is playing an important role in treatment of many patients and is effective in patients with triple-negative BC [91,92]. Pembrolizumab plus trastuzumab produced objective responses in patients with PD-L1-positive tumours with advanced trastuzumab-resistant HER2-positive BC [93]. Atezolizumab plus T-DM1 did not improve overall PFS in KATE2, but subgroup analyses suggested improved PFS in patients with HER2-positive advanced BC with

PD-L1 expression [94]. KATE3 will assess atezolizumab and T-DM1 in this subgroup (clinicaltrials.gov pending). The potential role of cancer immunotherapies is currently being evaluated in patients with HER2-positive EBC in the neoadjuvant (atezolizumab: IMpassion050, NCT03726879; APTneo, NCT03595592; pembrolizumab: Keyriched-1, NCT03988036; neoHIP, NCT03747120; durvalumab: Pro00020917, NCT03820141) and post-neoadjuvant settings (atezolizumab: ASTEFANIA, NCT04873362).

There is growing interest in potential combinations of HER2-targeted therapies and existing treatment modalities/agents. CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) and ETs are often used as first-line therapies for metastatic, HR-positive, HER2-negative BC [95-98]. PATINA (NCT02947685) is evaluating palbociclib, ET and trastuzumab-pertuzumab in ER-positive, HER2-positive disease.

There are several novel HER2-targeted conjugates, e.g., fam-trastuzumab deruxtecan-nxki (recently granted accelerated approval metastatic BC after DESTINY-Breast01) [99,100]; trastuzumab duocarmazine (being evaluated for metastatic BC) [101]. Fam-trastuzumab deruxtecan-nxki will be compared with T-DM1 in DESTINY Breast-05 (NCT04622319: EBC with residual invasive BC following neoadjuvant therapy).

Tucatinib increases 1-year PFS/OS with capecitabine and trastuzumab in heavily pre-treated patients with metastatic BC and CNS involvement (HER2CLIMB) [102]. An exploratory analysis in patients with intracranial involvement showed that objective response and duration of response were significantly longer with tucatinib

[103]. The potential of the tucatinib-T-DM1 combination to further improve outcomes and address the unmet medical need of CNS metastases will be evaluated in CompassHER2-RD (NCT04457596) [104].

Authors' recommendations

At present, the most important characteristics to be considered in risk-based clinical decision-making for the initial treatment of patients with HER2-positive disease include, in order of importance, tumour size, nodal status, HR status, histological grade, patient age, menopausal status and comorbidities.

Conclusions

The past decades have witnessed major advances in therapeutic options for patients with HER2-positive EBC, with HER2-targeted therapies as the well-established standard-of-care. Neoadjuvant pertuzumab–trastuzumab plus chemotherapy is standard-of-care for most patients with high-risk disease, in whom such therapy can eradicate the disease in the breast and axillary nodes. tpCR (ypT0/is, ypN0) is associated with improved long-term outcomes; however, traditional poor-prognostic factors, e.g., tumour size and baseline nodal status, remain important after pCR. Patients with tumours ≥2cm and/or node-positive disease at diagnosis who achieve pCR should continue pertuzumab–trastuzumab to complete a full 1-year course [20-23]. Residual invasive disease at surgery is a major decision point. KATHERINE's results provide direction for the treatment of women with residual invasive disease after surgery by showing that T-DM1 significantly increases IDFS and decreases risk of recurrence by 50%. Patients at lower risk of relapse (i.e., T1 tumours; no axillary involvement) should be considered candidates for de-escalated adjuvant

chemotherapy (paclitaxel-trastuzumab per APT, or perhaps T-DM1 per ATEMPT in the future). Ultimately, treatment recommendations should be consistent with local and international guidelines [73]. Further studies will continue to guide improvements in therapeutic efficacy and the optimisation of treatment for patients with HER2-positive EBC according to their risk of disease recurrence.

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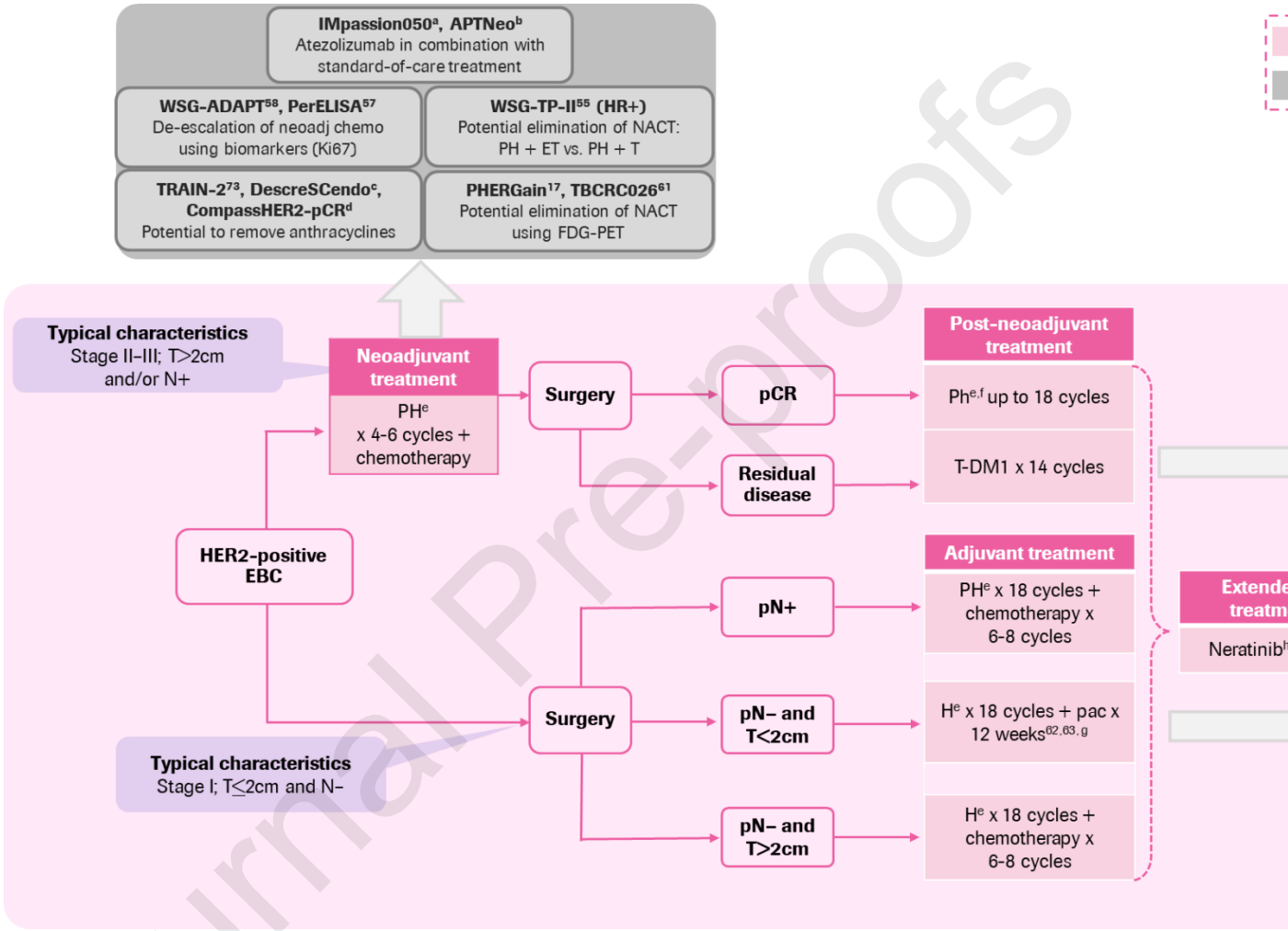
Figure legend (figure to be printed in colour)

Figure 1. Current treatment algorithm for HER2-positive EBC [20-23,25,30,32] **and planned/ongoing studies**



EBC: early breast cancer; ET: endocrine therapy; H: trastuzumab; HR: hormone-receptor; N: lymph node status;

NACT: neoadjuvant chemotherapy; p: pathological staging; P: pertuzumab; pac: paclitaxel; pCR: pathological complete response; SC: subcutaneous; T: tumour diameter; T-DM1: trastuzumab emtansine.

a. NCT03726879.

b. NCT03595592.

c. NCT04675827 (a sub-study of DecreSCendo will investigate the use of PH FDC SC for the treatment of patients who achieve a pCR following neoadjuvant therapy).

d. NCT04266249.

e. SC formulations improve patient and HCP convenience (see HannaH[78] and FeDeriCa[79] study results for data on H SC and PH FDC SC, respectively).

f. Recommended for patients with tumours ≥2cm and/or node-positive disease at diagnosis.

g. Guideline recommendations (NCCN, AGO, ESMO, St. Gallen) for the adjuvant use of trastuzumab with paclitaxel alone represent off-label use in this setting.

h. Neratinib has not been approved for use after PH or T-DM1.

i. NCT04622319.

j. NCT04457596.

k. Study not yet published on ClinicalTrials.gov.

Table 1. Optimising adjuvant therapy in patients with invasive non-metastatic HER2-positive early breast cancer (APHINITY [12,35]**)**

Patient characteristics	**Adjuvant regimen (No. of patients)**	**IDFS**				**OS**	
		3-year		**6-year**		**6-year**	
		%	**HRa (95% CI)**	**%**	**HRa (95% CI)**	**%**	**HRa (95% CI)**
Node-positive or node-negative disease with tumour >1cm[a]	Chemotherapy[b] + PH (2,400)	94.1	0.81 (0.66–1.00)	90.6	0.76 (0.64–0.91)	94.8	0.85 (0.67–1.07)
	Chemotherapy[b] + Placebo/H (2,404)	93.2		87.8		93.9	

CI, confidence interval; H, trastuzumab; HRa, hazard ratio; IDFS, invasive disease-free survival; OS, overall survival; PH, pertuzumab–trastuzumab

a. Patients with node-negative tumours 0.5–1.0cm in diameter were initially eligible if ≥1 high-risk feature was present: histological or nuclear grade 3, negativity for oestrogen and progesterone receptors, or age younger than 35 years. Under a protocol amendment that was added after 3655 patients had undergone randomisation, patients with node-negative disease were no longer eligible for enrolment.

b. Chemotherapy consisted of 3 or 4 cycles (q3w) of 5-fluorouracil plus either epirubicin or doxorubicin plus cyclophosphamide, followed by 3 or 4 cycles (q3w) of docetaxel or 12 weekly cycles of paclitaxel; 4 cycles (q3w or q2w) of cyclophosphamide plus either doxorubicin or epirubicin, followed by either 4 cycles (q3w) of docetaxel or 12 qw cycles of paclitaxel; or 6 cycles (q3w) of docetaxel plus carboplatin.

Table 2. De-escalation of neoadjuvant chemotherapy in patients with HER2-positive early breast cancer

Trial (n)	Patient characteristics	Neoadjuvant regimen	pCR, % (95% CI) (ypT0/is, ypN0)	3-year EFS, % (95% CI)	3-year OS, % (95% CI)
TRAIN-2 [18,75] mc, ol, r, ph3 (438)	Stage II–III	Pac/Cb/PH x 9	68 (61–74)	93.5 (90.4–96.6)	98.2 (96.4–100)
		FEC/PH x 3 → Pac/Cb/PH x 6	67 (60–73)	92.7 (88.3–96.2)	97.7 (95.7–99.7)
KRISTINE [54,55] mc, ol, r, ph3 (444)	Stage II–III cT2–4 (>2cm)/ cN0–3 /cM0 (>2cm)	TDM-1/P x 6	44.4	85.3 (80.5–90.1)	97.0 (94.6–99.4)
		Doc/Cb/PH x 6	55.7	94.2 (91.0–97.4)	97.6 (95.5–99.7)
WSG-TP-II [56] mc, ol, r, ph2 (207)	Hormone receptor-positive cT1c-T4a–c	ET/PH x 12 wks	24% (16–34)		
		Pac/PH x 12 wks	57% (47–67)		

Cb, carboplatin; CI, confidence interval; Doc, docetaxel; EFS, event-free survival; ET, endocrine therapy; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; HR+, hormone receptor-positive; mc, multicentre; ol, open-label; OS, overall survival; P, pertuzumab; ph, phase; Pac, paclitaxel; pCR, pathological complete response; PH, pertuzumab-trastuzumab; r, randomised

Table 3. De-escalation of adjuvant chemotherapy in patients with HER2-positive early breast cancer

Trial	Patient characteristics	Adjuvant regimen (No. of patients)	3-year DFS, % (95% CI)	7-year DFS, % (95% CI)	7-year OS % (95% CI)
APT [65,66] uc, mc, ph2	Stage I, tumour diameter ≤3cm	Pac/H x 12 wks → H x 40 weeks (406)	98.7 (97.6–99.8)	93 (90.4–96.2)	95 (92.4–97.7)
ATEMPT [67] r, mc, ph2	Stage I	TDM-1 q3w x 17 (383)	97.7 (96.2–99.3)		
		Pac/H x 12 wks → H x 39 weeks (114)	92.8 (87.8–98.1)		

CI, confidence interval; DFS, disease-free survival; H, trastuzumab; mc, multicentre; Pac, paclitaxel; r, randomised uc, uncontrolled

Highlights

- Risk of relapse must be evaluated to optimise treatment for HER2-positive early breast cancer.
- First, clinicians decide whether to offer neoadjuvant chemotherapy plus pertuzumab–trastuzumab.
- Patients with a pathological complete response continue HER2-targeted therapy to complete 18 cycles (before and after surgery).

- Patients with residual disease after standard-of-care neoadjuvant chemotherapy plus HER2-targeted therapy should receive post-neoadjuvant trastuzumab emtansine to complete 14 cycles (after surgery).
- For patients who undergo surgery first, treatment with adjuvant chemotherapy plus pertuzumab–trastuzumab is the standard of care for those patients with a higher risk of relapse.
- For patients with node-negative disease and tumours <2cm at presentation, paclitaxel for 12 weeks plus 18 cycles of trastuzumab might be a good option for the post-operative adjuvant therapy.

Declaration of interests

All authors received medical writing support from Roche for this article.

CJ reports personal fees from Roche, Novartis, Celgene, Exact Sciences, AstraZeneca, and Pfizer; and grants from Exact Sciences, during the conduct of the study.

PC is an employee of Genentech, Inc.

CEG reports non-financial support (unpaid advisory boards), grants and travel support from Genentech/Roche, Daiichi Sankyo, and AstraZeneca, during the conduct of the study; personal fees from Exact Sciences (paid advisory board) and Athenex (paid consultant); and research funding and non-financial support (writing support) from AbbVie, outside the submitted work.

LG reports personal fees (advisory board meetings) from Amgen, ADC Therapeutics, AstraZeneca, Celgene, Eli Lilly, G1 Therapeutics, Genentech, Inc., Genomic Health, MSD, Oncolytics Biotech, Odonate Therapeutics, Onkaido Therapeutics, Roche, Pfizer, Taiho Pharmaceutical, Sandoz, Seattle Genetics, Synthon and Zymeworks; grants from Pfizer, Zymeworks and Revolution Medicines; free consultancy for Forty Seven and Metis Precision Medicine; and paid consultancy for Menarini Ricerche, Synaffix, Novartis and Revolution Medicines, during the conduct of the study. In addition, LG has a patent, EPA 12195182.6 12196177.5-ROCHE, pending (co-inventor).

JG reports grants, personal fees and non-financial support for clinical trials, travel support, advisory boards and speakers' bureaus from Roche-Genentech, Eisai, Genomic Health and Pfizer; personal fees and non-financial support for clinical trials, travel support, advisory boards and speakers' bureaus from Novartis and Lilly; personal fees and non-financial support for clinical trials and advisory boards from Daiichi Sankyo and MSD; grants and personal fees for travel support, advisory boards and speakers' bureaus from Mylan; personal fees and non-financial support for travel support, advisory boards and speakers' bureaus from Pierre Fabre; and personal fees for advisory boards and speakers' bureaus from AstraZeneca, outside the submitted work.

ZM is an employee of Roche and owns stock in Roche Holding, Ltd.

EAP reports no other conflicts of interest pertinent to this work outside of the above-mentioned medical writing support.

AS reports research grants from AbbVie, Celgene and Roche; expert testimony for Roche and AstraZeneca; travel expenses from Celgene, Pfizer and Roche; honoraria from AstraZeneca, Celgene, Lilly, MSD, Novartis, Pfizer, Roche and Tesaro; and grants for medical writing from Roche, outside the submitted work.

SMT reports grants to her institute as principal investigator on studies from AstraZeneca, Eli Lilly, Merck, Nektar Therapeutics, Novartis, Pfizer, Genentech/Roche, Immunomedics, Exelixis, BMS, Eisai, NanoString, Cyclacel, Sanofi and Odonate Therapeutics; personal fees (honorarium for consultancy and/or advisory boards) from AstraZeneca, Eli Lilly, Merck, Nektar Therapeutics, Pfizer, Genentech/Roche, Immunomedics, BMS, Eisai, NanoString, Puma, Sanofi, Celldex, Odonate, Seattle Genetics, Silverback Therapeutics, G1 Therapeutics, AbbVie, Athenex, OncoPep, Kyowa Kirin Pharmaceuticals, Daiichi-Sankyo, CytomX and Samsung Bioepis, Inc.; personal fees from Exelixis; and travel expense reimbursement for advisory boards from Nektar Therapeutics, outside the submitted work.

MU reports compensation for his role as an advisor/consultant and for travel expenses to his institute from AbbVie, Amgen GmbH, AstraZeneca, BMS, Celgene GmbH, Daiichi Sankyo, Eisai GmbH, Lilly Deutschland, Lilly Int., MSD Merck, Mundipharma, Myriad Genetics, Odonate Therapeutics, Pfizer Germany, PUMA Biotechnology, Roche Pharma AG, Sanofi Aventis Deutschland GmbH, Teva Pharmaceuticals Ind. Ltd., Novartis, Pierre Fabre and Clovis Oncology.

AW has received personal fees from Pierre Fabre, Roche, Amgen, MSD, Boehringer-Ingelheim, Novartis, Pfizer, AstraZeneca, Athenex, Gerson Lehmann Group, Coleman Expert Network Group, Guidepoint global, Helios Medical, Simon-Kucher and Partners, Lilly and Daiichi Sankyo. After completion of this work AW is employed by AstraZeneca.

MP reports grants to her institute from Radius, AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Synthon and Servier; personal fees from AstraZeneca, Lilly, MSD, Novartis, Odonate Therapeutics, Pfizer, Roche-Genentech, Camel-IDS, Debiopharm, Menarini, Seattle Genetics, Immunomedics, Oncolytics (for being on the Scientific Board) and Immutep, outside the submitted work.