The Breast 62 (2022) S12–S16

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Neoadjuvant and adjuvant treatment of patients with HER2-positive early breast cancer☆

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ARTICLE INFO

Keywords:
HER2+ early breast cancer
Trastuzumab
Pertuzumab
T-DM1, neratinib

ABSTRACT

The availability of HER2-targeted therapy has dramatically improved patient outcome in HER2-positive (HER2+) early breast cancer (EBC) as recently demonstrated by the EBCTCTG metaanalysis on trastuzumab in HER2+ EBC: Adding trastuzumab to chemotherapy has reduced recurrence rates and breast-cancer related mortality by a third [1].

Today, neoadjuvant therapy has become standard of care for women with stage II or III tumors as pathological complete response (pCR) status after surgery can be used to individualize adjuvant systemic therapy. pCR is correlated with favorable patient outcome, particularly in hormone receptor (HR) negative HER2+ EBC, as demonstrated by the FDA meta-analysis. Moreover, for patients with non-pCR, 14 cycles of adjuvant T-DM1 have become a new adjuvant therapy standard based on the results of the KATHERINE trial. Primary surgery can be offered to patients with low tumor burden (cN0 cT1). For this low-risk subgroup, 12 weeks of adjuvant paclitaxel + trastuzumab for one year are correlated with excellent outcome based on the APT trial results. A multidisciplinary team is essential right from the beginning for optimal locoregional and systemic therapy in such a complex neoadjuvant – adjuvant continuum of care.

Clinical trials in HER2+ EBC are currently evaluating further therapy de-escalation in low-risk disease or patients with pCR whereas for patients with non-pCR, escalation trials are also ongoing. Newly approved drugs for HER2+ MBC like tucatinib or trastuzumab-deruxtecan or even immunotherapy combinations are being evaluated to improve upon efficacy of T-DM1 alone in the non-pCR setting. Regarding de-escalation, the WSG ADAPT trial demonstrated feasibility of avoiding overtreatment and individualizing neoadjuvant therapy without compromising outcome. Further de-escalation trials (e.g. DECRESCENDO, COMPASS-HER2) are currently ongoing.

1. Therapy standards

In HER2+ EBC, the benefit from anti HER2-therapy is substantial and largely independent of patient and tumor characteristics including hormone receptor status as demonstrated by the EBCTCG metaanalysis comprising 13864 patients recruited between 2000 and 2005 into 7 randomised trials [1]. Even though proportional risk reductions were similar between different nodal groups, absolute 5-year benefits from trastuzumab regarding recurrence were greatest in patients with higher nodal burden (N0: 5.7% N0; 1–3 lymph nodes (LN): 6.8%; 4+ LN: 10.7%). Regarding hormone receptor status, relative benefits were similar for patients with ER+ (HR 0.67) and ER-disease (HR 0.62) with observed absolute reductions in 10-year recurrence risk being slightly larger for ER- (10.1%) than for ER + disease (7.8%). ER-tumors had higher recurrence rates in the first 2 years whereas ER + tumors were associated with higher recurrence rates in years 5–9 [1]. These different recurrence dynamics over time may be important both for clinical follow-up care as well as for design of future trials in HER2+ EBC.

Since 2017, the St. Gallen consensus meetings have clearly highlighted the neoadjuvant approach as the preferred treatment option in tumors larger than 2 cm or with axillary lymph node involvement [2–4]. Today, neoadjuvant therapy has become standard of care for most patients as clinical response to neoadjuvant therapy as well as particularly pathological complete response (pCR) status after surgery can be used to individualize adjuvant systemic therapy [5]. Clinical response needs to be monitored closely under neoadjuvant therapy as early disease progression can be counteracted by a change of systemic therapy or treatment modality. Fortunately, early disease progression under

☆ This article is published as part of a supplement supported by St. Gallen Oncology Conferences.

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https://doi.org/10.1016/j.breast.2022.01.006
Received 14 July 2021; Received in revised form 4 January 2022; Accepted 11 January 2022
Available online 19 January 2022

state-of-the-art chemo- and anti-HER2 therapy is rare [6]. Thus, pCR status has become the important decision point of individualization of systemic therapy.

pCR is correlated with favorable patient outcome, particularly in hormone receptor (HR) negative HER2+ EBC, as demonstrated by the FDA meta-analysis [7]. Moreover, for patients with non-pCR, 14 cycles of adjuvant T-DM1 have become a new adjuvant therapy standard based on the results of the KATHERINE trial [8]. Primary surgery can be offered to patients with low tumor burden (cN0 cT1). For this low-risk subgroup, 12 weeks of adjuvant paclitaxel + trastuzumab for one year are correlated with excellent outcome as demonstrated by the single arm APT trial: After a median follow-up of 6.5 years, only 4 (1.0%) distant recurrences were seen with a 7-year overall survival (OS) of 95% (95% CI 92.4–97.7%) [9]. As all tumors in the APT trial were node-negative and the vast majority (91.1%) had a tumor size of 2 cm or less, a neoadjuvant approach should be considered for all larger N0 tumors or cN + tumors (see Fig. 1).

2. Neoadjuvant therapy

For neoadjuvant therapy, dual HER2-blockade with trastuzumab (H) and pertuzumab (P) together with a chemotherapy backbone was approved in 2013 by the FDA and in 2015 by the EMA based on results of the NeoSphere trial [10] together with the totality of supporting evidence at the time. The CLEOPATRA trial had already shown an OS advantage of H + P vs. H alone together with docetaxel chemotherapy in 1st line treatment of HER2+ metastatic breast cancer (MBC) [11]. Moreover, the adjuvant APHINITY trial had already been fully recruited by August 2013 [12].

Interestingly, the recently presented end-of-study analysis of CLEOPATRA confirmed the OS benefit of the earlier analyses with a median OS of 57.1 months in the trastuzumab and pertuzumab arm vs 40.8 months in the trastuzumab alone arm. The 8-year landmark OS rates were 37% vs 23%, respectively [13]. The updated APHINITY 6-year results have also confirmed the benefit from the adjuvant dual HER2 blockade [14] and will be discussed later.

pCR rates differ according to HR-status and are higher in HR- HER2+ than in HR + HER2+ (triple positive) EBC [7]. In TRYPHAENA, pCR (breast) rates with standard chemotherapies plus HP were around 70% in the HR- and around 50% in the HR + subset [15].

3. Chemotherapy backbone

Established neoadjuvant regimens in HER2+ EBC are either an anthracycline-taxane sequence plus HP or docetaxel-carboplatin plus dual HER2 blockade (TCbHP). Recently, the TRAIN2 study suggested that an anthracycline combination does not add efficacy neither regarding pCR [16] nor patient outcome [17] to a sequential taxane-platinum containing regimen with dual antibody blockade. In TRAIN2, comparable efficacy regarding EFS was observed in all clinically relevant subgroups, even in node-positive or stage III disease. Cardiac safety was significantly reduced in the anthracycline-containing arm, with LVEF declines not returning back to normal in about one third of patients. Moreover, two acute leucemia cases were observed in the anthracycline-containing arm [17]. Although TRAIN-2 is a rather small study with only 438 patients and uses a somewhat unusual chemotherapy regimen, the evidence for anthracycline-free chemotherapy in HER2+ EBC is much larger with studies like TRYPHAENA and BCIRG 006 also showing similar efficacy for anthracycline-free vs. anthracycline-containing regimens together with standard anti-HER2 therapy (see Table 1). In TRYPHAENA, cardiac safety was the primary endpoint: The incidence of symptomatic left ventricular systolic dysfunction (LVSD) and significant declines in the left ventricular ejection fraction (LVEF) was low in all arms: In the neoadjuvant setting, all grade LVSDs were seen in 5.6% of patients in the anthracycline (A)-containing arm with concomitant antibodies, in 4.0% in the A-containing arm with dual blockade only given together with the taxane, and in 2.6% in the A-free arm [15].

4. Adjuvant therapy according to pCR status

After neoadjuvant standard therapy, further adjuvant therapy can now be individualized based on pCR status: In patients with pCR, adjuvant anti-HER2 therapy consists of trastuzumab for the remainder of the one year of total anti-HER2 therapy. Patients with initially node-positive disease should receive dual blockade for the remainder of the year. There is still residual risk of recurrence in patients with pCR, particularly in those with high tumor burden at diagnosis as a GBG pooled analysis showed [20]. Extrapolation from the results of the adjuvant APHINITY trial suggest that continuing pertuzumab in the adjuvant setting is beneficial only in node-positive disease. After a

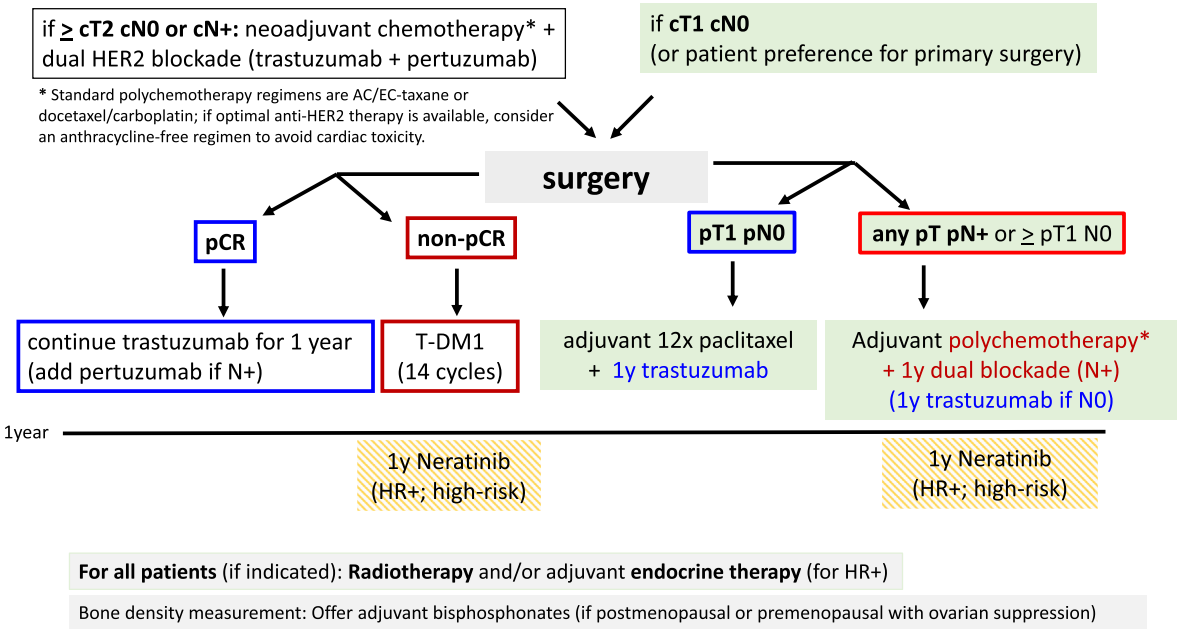

Fig. 1. Treatment algorithm in HER2-positive early breast cancer.

Table 1
Efficacy of anthracycline-free vs. anthracycline-containing regimens in HER2+ EBC.

Study	patients	w/o anthracylines	with anthracyclines	w/o anthracylines	with anthracyclines
		pCR	pCR	Survival	Survival
TRYPHAENA [15, 18]	225	ypT0/is: **66.2%** (TCbHP)	ypT0/is: **61.6%** (FEC-HP - > pac-HP) **57.3%** (FEC –> pac-HP)	3y DFS **90%** (TCbHP)	3y DFS: **87%** (FEC-HP - > T-HP); **88%** (FEC - > T-HP)
TRAIN-2 [16,17]	438	ypT0/is ypN0: **68%** (pacCb-HP)	ypT0/is ypN0: **67%** (FEC-HP - > pacCb-HP)	3y EFS **93.5%** (pacCb - > HP)	3y EFS **92.7%** (FEC-HP - > pacCb-HP)
BCIRG 006 [19]	3222	n.a.	n.a.	5y DFS **81%**; 5y OS **91%** (TCbH)	5y DFS **84%**; 5y OS **92%** (AC - > TH)

FEC = 5-Fluorouracil-Epirubicin-cyclophosphamid; pac = Paclitaxel; T = Docetaxel; Cb = Carboplatin; H = trastuzumab; P = pertuzumab n.a. = not applicable.

median follow-up of 74 months, 6-year iDFS was 91% for the pertuzumab arm and 88% for the placebo arm (HR 0.76; 95% CI 0.64–0.91). In the node-positive cohort, 6-year iDFS of 88% vs. 83%, respectively (HR 0.72; 95% CI 0.59–0.87). No benefit was seen in N0 disease. Benefit for pertuzumab was independent of hormone receptor status [14]. Nevertheless, together with the EBCTCG metaanalysis, the APHINITY trial with it two follow-up durations [12,14] clearly demonstrate that long-term follow-up is important in HER2+ EBC, particularly for capturing the full extent of therapy benefit in the HR + subgroup.

In patients with non-PCR, adjuvant T-DM1 substantially improves outcome vs. adjuvant trastuzumab and should thus be offered to these patients. The KATHERINE trial showed a substantial difference in 3-year iDFS of 88.3% in the T-DM1 arm and 77% in the trastuzumab arm (HR 0.50; 95% CI 0.39–0.64; $p < 0.001$) in patients with non-pCR after a minimum of 6 cycles of neoadjuvant therapy with at least 9 weeks of a taxane and 9 weeks of trastuzumab therapy. Eligible Patients had an initial tumor burden of at least cT1c cN0 or all cN+; after neoadjuvant therapy about 22% had only minimal residual invasive disease of ypN0 ypT1a/b or ypT1mic [8]. iDFS benefit was seen in KATHERINE independent of adjuvant endocrine therapy or radiotherapy. Of 845 patients with available paired tissues samples from initial diagnosis and non-pCR, 70 (8.3%) had HER2-residual disease. Benefit from T-DM1 was observed independent of HER2 status in the non-pCR specimen as in thi small subgroup, no iDFS events were seen in T-DM1-treated patients vs. 11 in those with trastuzumab therapy [21].

5. Duration of anti-HER2 therapy

The current standard of care is 12 months of anti-HER2 therapy. While longer duration of the same anti-HER2 therapy does not increase efficacy as demonstrated by the HERA trial for 2y vs. 1y of trastuzumab [22], the data on shorter trastuzumab duration is controversial. Unfortunately, the recent EBCTCG metaanalysis could only include the FinHER trial with 9 weeks of trastuzumab for a patient-level analysis. A post-hoc metaanalysis of published study data on shorted duration showed fewer events for 12 months vs. 6 months duration – yet the authors conclude that only a patient level analysis may be able clarify risks and benefits for individual patient groups [1]. At ESMO 2021, Helena Earl presented a patient level metaanalysis of 5 trials exploring shorter adjuvant trastuzumab duration and showed that a 6-month duration is non-inferior to 12 months whereas a 9-week duration is not [23]. Among the individual trials, only PERSEPHONE has reached its non-inferiority endpoint. Yet, for some clinically relevant subgroups (e.g. concurrent trastuzumab, neoadjuvant therapy), exploratory hazard ratios do not show non-inferiority [24]. Subgroup analyses from the metaanalysis have not yet been presented. Thus, for the time being, one year of trastuzumab therapy remains standard of care. Nevertheless, the results of the shorter vs. longer duration trials may help to counsel individual patients if trastuzumab is not available for a whole year or cannot be tolerated. As treatment standards in HER2+ EBC have changed over time, in addition to subgroup analyses from large adjuvant trials in unselected populations, results from ongoing trials looking at de-escalating adjuvant anti-HER2 therapy duration after pCR are needed to change clinical practice. Optimal duration of anti-HER2 therapy remains an important global issue in order avoid unnecessary clinical but also financial toxicity.

6. Extended adjuvant anti-HER2 therapy

The phase III ExteNET trial (n = 2840) showed benefit for an additional year of anti-HER2 therapy with neratinib after one year of neoadjuvant/adjuvant trastuzumab-based therapy. In the population reflecting the EMA approval of HR + HER2+ within 1 year post-trastuzumab, 5-year iDFS benefit for neratinib was 5.1% (HR 0.58; 95% CI 0.41–0.82) and even 7.4% for patients with non-pCR (HR 0.60; 95% 0.33–1.07) [25]. As patients in the ExteNET trial had neither received pertuzumab nor T-DM1, absolute benefit after modern neoadjuvant and post-neodjuvant anti-HER2 therapy may be smaller. Nevertheless, neratinib offers an additional treatment option in high-risk HR + HER2+ EBC. Patients need to be realistically informed and potential benefit weighed against possible side effects.

7. Future developments

Clinical trials in HER2+ EBC are currently evaluating further therapy de-escalation in low-risk disease or patients with pCR whereas for patients with non-pCR, escalation trials are also ongoing.

Newly approved drugs for HER2+ MBC like tucatinib or trastuzumab-deruxtecan, immunotherapy combinations or addition of endocrine-based therapy in HR + HER2+ EBC are being evaluated to improve upon efficacy of T-DM1 alone in the non-pCR setting. T-DXd is currently also developed in the neoadjuvant setting to evaluate whether this promising antibody-drug conjugate can – at least partly - replace standard chemo- and anti HER2 therapy.

Regarding de-escalation, the WSG ADAPT trial demonstrated feasibility of avoiding overtreatment and individualizing neoadjuvant therapy: In the HER2+/HR-subtrial, total pCR was about 90% with 12 weeks of paclitaxel weekly plus dual HER2-blockade (HP). In the HER2+/HR + subtrial (ADAPT TP), pCR rates were around 40% with 12 weeks of T-DM1 ± endocrine therapy [26]. Recent survival data from ADAPT TP with 93% 5-year DFS demonstrated that pCR even after a de-escalated 12-week therapy is relevant for patient outcome. Moreover, additional systemic chemotherapy does not seem to improve outcome after pCR obtained with a de-escalated regimen [27]. With only 12 weeks of neoadjuvant paclitaxel and dual HER2 blockade, WSG ADAPT HER2+/HR-showed a 90.5% pCR rate in HR-negative disease [28], and WSG TP II showed a pCR rate of 57% in HR-positive disease [29].

The ADAPT experience has clearly demonstrated that de-escalation trials are safe and benefit patients as well as that a pCR obtained after a de-escalated regimen is clinically meaningful. Consequently, ongoing international trials such as DECRESCENDO or Compass-HER2 are looking at therapy individualization according to pCR status after a short de-escalated neoadjuvant regimen of 12 weeks of paclitaxel + HP [30].

Regarding chemotherapy-free regimens, evidence is accumulating that pCR rates are only meaningful in preselected patients and that such

trial should not be performed in unselected cohorts. Currently strategies investigating anti-HER2 therapies alone or in combination with endocrine-based therapies are looking at pre-selecting patients by biomarkers such as HER2-E phenotype or early therapy response determined either by a biopsy after 1–2 cycles or by molecular imaging.

For clinical practice, it is important to point out that - given the excellent outcomes achieved with standard therapy regimens in HER2+ EBC - de-escalation attempts in daily routine must be based on current guidelines and available evidence or be performed within clinical trials.

8. Conclusions

Neoadjuvant therapy has become the standard of care in HER2+ EBC, at least in $\geq$ 2 cm N0 or all N+ disease. A summary of current therapy standards for the neoadjuvant and adjuvant setting can be found in Fig. 1. While patients with pCR will have a very favorable outcome with adjuvant continuation of trastzumab (+/− pertuzumab), adjuvant T-DM1 offers an important escalation strategy in case of non-pCR. A multidisciplinary team is essential right from the beginning for optimal locoregional and systemic therapy in such a complex neoadjuvant – adjuvant continuum of care.

Declaration of competing interest

NH received honoraria for lectures and/or consulting from Astra Zeneca, Daiichi-Sankyo, Exact Sciences, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, SeaGen, NH is a co-director of the West German Study Group.

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