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Escalating and de-escalating treatment in HER2-positive early breast cancer

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ABSTRACT

The current standard adjuvant systemic treatment of early HER2-positive breast cancer consists of chemotherapy plus 12 months of trastuzumab, with or without endocrine therapy. Several trials have investigated modifications of the standard treatment that are shorter and less resource-demanding (de-escalation) or regimens that aim at dual HER2 inhibition or include longer than 12 months of HER2-targeted treatment (escalation). Seven randomized trials investigate shorter than 12 months of trastuzumab treatment duration. The shorter durations were not statistically inferior to the 1-year duration in the 3 trials with survival results available, but 2 of the trials were small and 1 had a relatively short follow-up time of the patients at the time of reporting. The pathological complete response (pCR) rates were numerically higher in all 9 randomized trials that compared chemotherapy plus dual HER2 inhibition consisting of trastuzumab plus either lapatinib, neratinib, or pertuzumab with chemotherapy plus trastuzumab as neoadjuvant treatments, but the superiority of chemotherapy plus dual HER2-inhibition over chemotherapy plus trastuzumab remains to be demonstrated in the adjuvant setting. One year of adjuvant trastuzumab was as effective as 2 years of trastuzumab in the HERA trial, and was associated with fewer side-effects. Extending 1-year adjuvant trastuzumab treatment with 1 year of neratinib improved disease-free survival in the ExteNET trial, but the patient follow-up times are still short, and no overall survival benefit was reported. Several important trials are expected to report results in the near future and may modify the current standard.

Introduction

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase encoded by the *ERBB2* gene, located at 17q12. *ERBB2* amplification leads to overexpression of the HER2 protein [1,2]. HER2-positive breast cancers frequently give rise to distant metastases at visceral sites as compared to luminal A cancers [3,4]. In the era that preceded the modern systemic therapies even small node-negative HER2-positive cancers ⩽2 cm in diameter were associated with a 20–30% risk for distant metastases [5,6]. HER2-positive breast cancers are usually identified with either presence of HER2 protein overexpression in breast tumor tissue at immunohistochemistry or *ERBB2* amplification at *in situ* hybridization. The HER2-status of the primary breast tumor and paired distant metastases are discordant in about 10% of the patients [7,8]. *ERBB2* is amplified in 15–25% of breast carcinomas, the frequency being influenced by the criteria used to define HER2-positivity [9].

Patients with early HER2-positive breast cancer benefit from HER2-targeted systemic therapy. The only exception is patients with small (⩽5 mm) node-negative cancer, when local therapy alone is considered sufficient [10,11]. Patients with HER2-positive cancer that expresses estrogen receptors (ER) and/or progesterone receptors (PgR) are treated with adjuvant endocrine therapy as other patients with steroid hormone receptor-positive breast cancer [10].

This review discusses the current systemic adjuvant and neoadjuvant HER2-targeted treatments for early HER2-positive breast cancer, and the attempts to modify the treatment by either making it shorter, less toxic, and less resource-demanding (de-escalation), or more effective with dual HER2 inhibition or extending the treatment duration (escalation). These 2 strategies are not necessarily mutually exclusive, as dual HER2-inhibition may potentially be integrated in regimens of short duration.

Current standard treatment

The currently recommended standard adjuvant treatment for patients with early HER2-positive breast cancer is chemotherapy

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plus trastuzumab administered for 1 year. Chemotherapy consists usually of a few cycles of an anthracycline-containing regimen followed by a taxane, the latter given concurrently with trastuzumab. Docetaxel, carboplatin, and trastuzumab (TCH) is an option, particularly for patients who are unsuitable for anthracycline-containing treatment [10,12]. Even patients with small HER2-positive cancer benefit from adjuvant trastuzumab [13], but anthracyclines may not be needed when treating node-negative cancer ⩽1 cm in diameter, as such patients have a high disease-free survival (DFS) rate when treated with 1 year of trastuzumab plus paclitaxel [14] or 4 cycles of docetaxel and cyclophosphamide [15].

Adjuvant trastuzumab was first investigated in 4 large randomized trials as the treatment of early HER2-positive breast cancer, the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31, the North Central Cancer Treatment Group (NCCTG) trial N9831, HERA, and the Breast Cancer International Research Group (BCIRG) trial 006 [16,17,12]. The same trastuzumab dose (2 mg/week) and the same duration (12 months) were selected for evaluation in all 4 trials. The 12-month duration was studied also in 2 smaller randomized adjuvant trials, the NOAH [18] and the PACS 04 [19] trials. The choice of the 12-month duration for study was arbitrary [20], and no clinical or preclinical evidence to support this duration existed. The Food and Drug Administration (FDA) approved adjuvant trastuzumab in 2006, as there was compelling evidence for efficacy and the safety profile was favorable. In the absence of data from other durations than the 12-month duration, the 1-year duration became the standard.

In a Cochrane Breast Cancer Group literature search that included 8 randomized controlled adjuvant trials and 11,991 patients, the combined hazard ratios (HRs) for DFS and overall survival (OS) favored very significantly the trastuzumab-containing regimens over the same chemotherapy without trastuzumab. There were 40% fewer cancer recurrences in the groups treated with trastuzumab (HR 0.60, 95% confidence interval [CI] 0.51–0.71) and 34% fewer deaths (HR 0.66, 95% CI 0.57–0.77) [21]. The favorable effect of adjuvant trastuzumab on survival appears durable. In the planned joint analysis of the B-31 and the N9831 trials based on a median follow-up time of 8.4 years of the patients, adding trastuzumab to chemotherapy improved the 10-year OS rate from 75% to 84% (a relative improvement of 37% as compared with the chemotherapy only group) and the 10-year DFS rate from 62% to 74% (a relative improvement of 40%) [22].

Trastuzumab is generally well tolerated, but periodical monitoring of the cardiac left ventricular ejection fraction (LVEF) is considered mandatory as trastuzumab increases the risk of congestive heart failure (CHF). In a meta-analysis the absolute overall risk for high-grade CHF among 18,111 patients who participated in 6 randomized controlled adjuvant trials evaluating trastuzumab was 1.4%, and the relative risk as compared with the control groups 3.2 [23]. Patients treated with adjuvant trastuzumab for 2 years had a higher risk for cardiac adverse effects than those treated for 1 year [24], whereas a 9-week course of trastuzumab was associated with no detectable risk [23]. Another overview analysis found an increased risk for severe heart failure in patients treated with trastuzumab-based versus non-trastuzumab-based regimens of 2.5% and 0.4%, respectively (a relative risk of 5.11) [21]. Almost all cardiac failures are detected within the first 2 years since starting adjuvant trastuzumab. In one study, follow-up for a median of 9.2 years revealed only 2 additional diagnoses of CHF among 1046 patients after the first 3 years of follow-up, indicating that late onset of trastuzumab-related cardiac failure is rare [25]. The LVEF recovers in most patients who develop heart failure after trastuzumab discontinuation and initiation of therapy for heart failure [24–26]. A low LVEF, hypertension medication, coronary artery disease, and age have been identified as risk factors for trastuzumab-related cardiac failure [25–27]. Yet, as geriatric patients were underrepresented in the major adjuvant trials [28] and those with cardiac risk factors were excluded, the risk may be higher in population-based studies [29]. In a cohort study among breast cancer patients aged >65 and with full Medicare coverage, the rate of CHF was 29.4% among trastuzumab users as compared to 18.9% among the non-users [27].

Trastuzumab chemotherapy partners

Administration of some chemotherapy agents concomitantly with trastuzumab likely improves efficacy substantially. Preclinical studies suggest that docetaxel, vinorelbine, cyclophosphamide, and platinum salts are synergistic with trastuzumab [30,31]. The combination of docetaxel plus trastuzumab has been compared to single-agent trastuzumab in 2 randomized trials in advanced HER2-positive breast cancer [32,33]. In these 2 trials, the patients allocated to docetaxel plus trastuzumab had a median time to disease progression of 14.6 and 9.4 months compared to only 3.7 and 3.4 months, respectively, in the groups allocated to single-agent trastuzumab, suggesting that adding concomitant docetaxel to trastuzumab approximately triples the time to progression compared to trastuzumab alone. Furthermore, the only randomized trial (N9831) that compared concomitant administration of adjuvant trastuzumab with chemotherapy (weekly paclitaxel) to sequential administration found the 5-year DFS rate to favor concomitant administration (84.4% vs. 80.1%, respectively) [34]. These data suggest that the chemotherapy partners given concomitantly with trastuzumab are important for the overall regimen efficacy. With the exception of the B-31 and the N9831 trials that shared 2 treatment arms [16], the companion chemotherapy agents varied in the randomized trials that evaluated adjuvant trastuzumab, and in the HERA and the PACS 04 trials all trastuzumab was administered only after chemotherapy completion [17,19].

Randomized de-escalation trials

Seven randomized trials ask the question whether comparable efficacy to 1-year adjuvant trastuzumab can be achieved with a shorter regimen, but with fewer side-effects (Table 1). In 4 of these trials all trastuzumab is administered concomitantly with chemotherapy in the experimental arm in an attempt to exploit drug synergism (FinHer, E2198, SOLD, and Short-HER trials), and 3 trials compare 6-month to 12-month duration of trastuzumab (the Hellenic trial, PHARE, and PERSEPHONE) [35–42].

FinHer was the first randomized trial to evaluate a shorter than the 12-month duration of adjuvant trastuzumab, and may be considered as the first de-escalation trial. FinHer accrued 1010 patients with early breast cancer from 17 centers in Finland in October 2000 to September 2003. The patients were assigned to either 3 3-weekly cycles of docetaxel or weekly vinorelbine, each followed by 3 3-weekly cycles of FEC. The 232 patients with HER2-positive disease had a second randomization to weekly trastuzumab, given upfront and concomitantly with either docetaxel or vinorelbine, or to observation [35]. The selection of docetaxel and vinorelbine as the companion agents with trastuzumab was based on preclinical data that suggested drug synergism [30]. The duration of 9 weeks of HER2-targeted therapy resulted from the duration of 3 3-weekly given chemotherapy cycles. The Finnish Breast Cancer Group sponsored the trial, and funding for trastuzumab was obtained from the government budget of Finland. Somewhat unexpectedly, the patients treated with 9-week trastuzumab plus docetaxel or vinorelbine had a comparable hazard ratio for cancer recurrence (0.42, 95% CI 0.21–0.83) as was achieved in the B-31, N9831, and HERA trials with 1-year duration of trastuzumab [35], suggesting that the brief administration of trastuzumab with

Table 1
Randomized trials evaluating less than 12-month duration of adjuvant trastuzumab.

Study	Target group	Groups	Patients (n)	Regimens	Median follow-up (years)	DFS/DDFS events (n)	Died (n)	DFS/DDFS	Overall survival
FinHer [35,36]	pN+, or high-risk pN0	T 9 wks	116	D/Vix3 + $T_{9\ wk}$ → FECx3	5.2	20	12	5-y 83.3%	5-y 91.3%
		No T	116	D/Vix3 → FECx3		30	21	5-y 73.0%	5-y 82.3%
								HR 0.65,	HR 0.55,
								$P = 0.12$	$P = 0.094$
E2198 [37]	Stage	T 12 mo	112	$wP_{12\ wk}$ + $T_{10\ wk}$ → ACx4 → $T_{12\ mo}$	6.4	33	23	5-y 73%	5-y 83%
	II and IIIA	T 10 wk	115	$wP_{12\ wk}$ + $T_{10\ wk}$ → ACx4		27	18	5-y 76%	5-y 89%
								HR 0.77,	HR 0.73,
								$P = 0.31$	$P = 0.32$
SOLD	pN+, or	T 12 mo	2136	Dx3 + $T_{9\ wk}$ → FECx3 → $T_{42\ wk}$	N.A.	N.A.	N.A.	N.A.	N.A.
	high-risk pN0	T 9 wks		Dx3 + T_{9wk} → FECx3					
Short-HER [38]	pN+, or	T 12 mo	1200	AC/ECx4 → D/Px4 + $T_{12\ wk}$→ $T_{42\ wk}$	N.A.	N.A.	N.A.	N.A.	N.A.
	high-risk pN0	T 9 wks		Dx3 + $T_{9\ wk}$ → FECx3					
Hellenic trial [39]	pN + or	T 12 mo	241	FECx4 → Dx4 + $T_{12\ mo}$	4	17	10	3-y 95.7%	N.A.
	high-risk pN0	T 6 mo	240	FECx4 → Dx4 + $T_{6\ mo}$		28	8	3-y 93.3%	N.A.
								HR 1.57,	$P = 0.436$
								$P = 0.137$	
PHARE [40]	Stage	T 12 mo	1691	Chemotherapy ⩾ 4 cycles → $T_{12\ mo}$	3.5	175	66	2-y 93.8%	N.A.
	I–III	T 6 mo	1693	Chemotherapy ⩾ 4 cycles → $T_{6\ mo}$		219	93	2-y 91.1%	N.A.
								HR 1.28,	HR 1.46
								$P = 0.29$	
PERSE-PHONE [42]	pN0 or pN+	T 12 mo	4000	Chemotherapy → $T_{12\ mo}$	N.A.	N.A.	N.A.	N.A.	N.A.
		T 6 mo		Chemotherapy → $T_{6\ mo}$					

DFS: disease-free survival; DDFS: distant disease-free survival; T: trastuzumab; D: docetaxel; Vi: vinorelbine; FEC; fluorouracil, epirubicin, cyclophosphamide; HR: hazard ratio; wP: weekly paclitaxel; AC: doxorubicin plus cyclophosphamide; N.A.: not available; EC: epirubicin plus cyclophosphamide; P: paclitaxel.

synergistic chemotherapy agents warrants further research. In FinHer, 1 patient in the trastuzumab group and 2 patients in the observation group had symptomatic heart failure [36].

The E2198 trial accrued 227 patients with axillary-node positive, stage II or IIIA HER2-positive breast cancer in the USA in 1999 to 2000. The patients were randomly assigned to weekly paclitaxel for 12 weeks plus weekly trastuzumab given for 10 weeks concomitantly with paclitaxel, followed by 4 3-weekly cycles of doxorubicin plus cyclophosphamide (AC) or to the same therapy plus 1 year of trastuzumab administered after completion of chemotherapy (Table 1). The primary objective was to evaluate safety, particularly CHF. DFS and OS were secondary objectives. Very few patients had CHF (4 in the 1-year trastuzumab group and 3 in the 10-week group). DFS or OS did not differ significantly between the groups after a median of 6.4 years of follow-up [37].

The Synergism Or Long Duration (SOLD) trial (NCT00593697) is the follow-up trial of FinHer with a design that resembles that of E2198, except that 3 3-weekly cycles of docetaxel are administered in place of weekly paclitaxel, FEC (fluorouracil, epirubicin, cyclophosphamide) in place of AC, and the duration of trastuzumab given concomitantly with a taxane is 9 weeks instead of 10 weeks (Table 1). The only difference between the 2 allocation groups in SOLD is post-chemotherapy trastuzumab, which is not administered in the experimental arm. The target population consists of patients with either node-negative or node-positive breast cancer; node-negative patients with breast cancer diameter ⩽1 cm are excluded. The primary objective is DFS. SOLD is a non-inferiority trial. Accrual was completed in December 2014 with 2136 patients entered from 7 countries. The first results, based on a minimum median follow-up of approximately 5 years, are expected in 2017.

The Short-HER trial (NCT00629278) compares the most effective N9831 trial arm (ACx4, followed by taxane plus concomitant trastuzumab for 12 months) with the docetaxel arm of the FinHer trial (Table 1). Some variability in the chemotherapy regimens in the 12-month trastuzumab arm is allowed (either doxorubicin or epirubicin, and either paclitaxel or docetaxel may be administered). Besides trastuzumab administration duration, also the number of scheduled chemotherapy cycles and the sequence of taxanes and anthracyclines differ between the arms [38]. The trial has completed accrual with approximately 1200 patients entered. The first results are anticipated in 2017.

Three randomized trials compare 6–12 months of adjuvant trastuzumab. Two of these trials, the Hellenic trial [39] and PHARE [40], have reported results, but the median follow-up times of the patients were still relatively short at the time of reporting.

The Hellenic Oncology Research Group trial assigned 481 patients with node-positive or high-risk node-negative HER2-positive breast cancer to 4 cycles of 2-weekly FEC (epirubicin dose 75 mg/m^2), followed by 4 cycles of 2-weekly docetaxel (75 mg/m^2) with leukocyte growth factor support between 2004 and 2012 [39]. Trastuzumab was started concomitantly with docetaxel, and then continued based on random allocation either for 12 or 6 months. The patients were followed up for a median of approximately 4 years. The 3-year DFS rates were high in both groups (Table 1). The hazard ratio tended to favor the standard duration group, but there was no significant difference between the groups in DFS. The HR for OS was not reported, but there was no statistical difference in OS between the groups, and numbers of patients who died were small (8 in the 6-month group; 10 in the 12-month group). Only 2 patients had cardiac toxicity.

A total of 3384 patients with stage I to III HER2-positive breast cancer were entered from 156 French sites in 2006 to 2010 to PHARE. The patients were required to have received at least 4 cycles of chemotherapy. Randomization took place after completion of chemotherapy, and the patients were assigned either to continue trastuzumab up to 12 months or to stop at 6 months of

treatment. The chemotherapy regimens were variable, but most patients were treated with an anthracycline and a taxane-containing regimen. Most patients received trastuzumab concomitantly with chemotherapy (12-month group, 57%; 6-month group, 56%). No re-staging was done at the time of randomization. After a median follow-up time of 3.5 years, 175 and 219 patients had cancer recurrence or had died, leading to a hazard ratio of 1.28 (95% CI 1.05–1.56) in favor of the 12-month group. This difference was not significant, as the trial was designed as a non-inferiority trial with a non-inferiority margin of 1.15, leading to a *P* value of 0.29. The numbers of deaths also favored numerically the longer duration. In subgroup analyses DFS was similar among patients with ER-positive cancer and among those treated with concomitant chemotherapy and trastuzumab, whereas patients with ER-negative cancer who were treated with sequential chemotherapy and trastuzumab benefitted from the 12-month duration of trastuzumab [40]. The incidence of CHF was 0.7% and 0.5% in the 12 and 6-month groups, respectively, and the incidence of cardiac dysfunction 5.9% and 3.4% ($P = 0.001$) [41]. Overall, PHARE thus failed to show inferiority of the 6-month administration of trastuzumab.

The PERSEPHONE trial (NCT00712140) is a sister trial of PHARE that aims to accrue 4000 patients with early breast cancer from multiple centers located in the U.K. [42]. The patients receive standard chemotherapy regimens as per institutional practice either as adjuvant chemotherapy or neoadjuvant chemotherapy, and either concurrently with or sequentially to trastuzumab, and trastuzumab for either 6 or 12 months based on random allocation. Randomization occurs before the patient receives the 10th cycle of trastuzumab. PERSEPHONE is a non-inferiority trial to detect 3% non-inferiority in terms of DFS and OS. No results are yet available, but are expected in 2017.

In sum, while standard duration of adjuvant trastuzumab remains as 12 months, non-inferiority of the shorter regimens could not be demonstrated in E2198, the Hellenic trial, or in PHARE. Yet, the results of the Hellenic trial, and particularly those of PHARE, tend to favor the 12-month treatment. The median follow-up time of the study patients is still relatively short in these trials. In the HERA trial that compared 1-year to 2-year adjuvant trastuzumab treatment, the early survival results at about 3 years from the date of randomization appeared to favor the 2-year group, but this difference between the groups disappeared with longer follow-up [43], suggesting that in some patients trastuzumab prohibits the growth of occult metastases, but may not eradicate them. In PHARE, the difference in favor of the 12-month group was detected in the subgroup with ER-negative disease treated with sequential chemotherapy and trastuzumab, which timing of trastuzumab administration is no longer preferred [10].

Besides the timing and duration of trastuzumab administration, the partner drugs to trastuzumab varied between the trials. Hypothetically, the duration of trastuzumab administration might become relatively less important as the efficacy of the drug combinations increase. The timing of randomization also varied. While in the FinHer, E2198, SOLD, and the Hellenic trial randomization was carried out prior to starting systemic therapy, randomization was done after completion of chemotherapy in PHARE, and prior to the 10th trastuzumab cycle in PERSEPHONE. The timing of randomization may influence the study patient populations, as the patients who progress rapidly or who do not tolerate the therapy become excluded when randomization is done after chemotherapy. Staging might be more rigorous when the key staging examinations are mandated by a study protocol, these possibly preventing patients with overt undetectable metastases from entering the study. As patients with overtly metastatic disease benefit from maintained HER2-targeted therapy [44,45], less rigorous staging might favor the longer durations of adjuvant HER2-targeted treatments.

Randomized escalation trials with extended duration of HER2-targeted therapy

Two large randomized trials have investigated longer than 12 months of adjuvant HER2-targeted therapy as the treatment of early breast cancer, the HERA [43] and the ExteNET [46] trials (Table 2).

HERA is the only trial that has evaluated longer than the 12-month duration of adjuvant trastuzumab. In 2001 to 2005, 1552 patients with early HER2-positive breast cancer were allocated to 1 year of trastuzumab and 1553 patients to 2 years of trastuzumab after completion of chemotherapy. The patients had been followed up for a median of 8 years at the time of the first reporting of the results. At this mature stage, 367 patients in each group had cancer recurrence or had died resulting in a HR of 0.99 (95% CI, 0.85–1.14). The numbers of patients who died were also similar in the 2 groups, 186 in the 12-month group and 196 in the 24-month group. More patients in the 24-month group had grade 3–4 adverse events (20.4% vs. 16.3%) and decreases in the LVEF (7.2% vs. 4.1%) as compared to the 1-year group [43]. These results suggest that 2 years of adjuvant trastuzumab cannot be recommended for the standard therapy, as 12 months of trastuzumab is equally effective, but better tolerated and less costly.

Neratinib is an orally administered, irreversible inhibitor of HER1, HER2, and HER4. In the ExteNET trial, 2840 women were assigned in 2009 to 2011 at the time when they had completed 12 months of adjuvant trastuzumab to either neratinib or placebo, each to be continued for another 12 months [46]. The 2-year DFS was 93.9% in the neratinib group and 91.0% in the placebo group with a HR of 0.67 (95% CI, 0.50–0.91, $P = 0091$; Table 2). The 3-year DFS rates, reported recently, were 92.0% and 89.9%, respectively (HR 0.74, 95% CI 0.56–0.96; $P = 0.023$) [47]. In subgroup analyses neratinib was more effective in the subset of ER-positive cancer, whereas no difference in efficacy was found among patients with ER-negative disease. These results are interesting, as neratinib might eradicate some cancers that are resistant to trastuzumab, and might be more effective for some tumors that depend also on ER-signaling. However, the median follow-up time of the patients is still short, and no OS data were reported. Neratinib appears to have little cardiac toxicity [46]. The most troublesome side-effect is diarrhea, but this occurs usually only in the beginning of neratinib treatment and can be managed effectively with prophylactic loperamide.

Escalation with dual HER2 inhibition

Dual inhibition of HER2 has emerged as a method to improve the pathological complete response (pCR) rates achieved with neoadjuvant therapy, although the use of pCR to compare treatments for survival endpoints is controversial [48–51]. Dual inhibition of HER2 has been attempted either with trastuzumab plus a small molecule tyrosine kinase inhibitor (lapatinib, neratinib, or afatinib), or with 2 different HER2-targeting antibodies. Trastuzumab and pertuzumab bind at different sites on the extracellular portion of HER2 (domains 4 and 2, respectively) [52]. While trastuzumab inhibits ligand independent signaling of HER2 and cleavage of HER2 to p95HER2 (a truncated but constitutively active form), pertuzumab prevents HER2 from forming dimers with other HER2 family proteins. Both antibodies elicit antibody-dependent cell-mediated cytotoxic (ADCC) effects [53–57]. In the first-line treatment of advanced HER2-positive breast cancer dual inhibition of HER2 was more effective than inhibition with trastuzumab alone in the CLEOPATRA trial, where the combination of docetaxel plus trastuzumab plus pertuzumab resulted in 15.7 months longer OS as compared with docetaxel plus trastuzumab plus placebo

Table 2
Randomized adjuvant or neoadjuvant/adjuvant trials evaluating longer than 12-month duration of HER-targeted therapy or dual HER2 inhibition.

Study	Target group	Groups	Patients (n)	Regimens	Median follow-up (years)	DFS/EFS events (n)	Died (n)	DFS/EFS/PFS	Overall survival
HERA [43]	pN + or pN0 with T > 1 cm	T 12 mo	1552	Chemo ⩾ 4 cycles → $T_{12\ mo}$	8	367	186	8-y 76.0%	86.4%
		T 24 mo	1553	Chemo ⩾ 4 cycles → $T_{24\ mo}$		367	196	8-y 75.8% HR 0.99, $P = 0.86$	87.6% HR 1.05, $P = 0.63$
ExteNET [46,47]	Stage I–III	T	1420	Chemo → $T_{12\ mo}$ → $Placebo_{12\ mo}$	2.0	109	N.A.	2-y 91.6%	N.A.
		T → N	1420	Chemo → $T_{12\ mo}$ → $Neratinib_{12\ mo}$		70	N.A.	2-y 93.9% HR 0.67, $P = 0.0091$	N.A.
ALTTO [74]	pN+, or pN0 with T ⩾ 1 cm	T	2097	Chemo → $T_{52\ wk}$	4.5	301	135	4-y 86%	4-y 94%
		T + L	2093	Chemo → L + $T_{52\ wk}$		254	106	4-y 88%	4-y 95%
		T → L	2091	Chemo → $T_{12\ wk}$ → $L_{34\ wk}$		284	119	4-y 87%	4-y 95%4-y 93%
		L	2100	Chemo → $L_{52\ wk}$		366	168	4-y 82% $HR_{T+L\ vs.\ T}$ 0.84, $P = 0.048$; $HR_{T\text{-}L\ vs.T}$ 0.96, $P = 0.61$; $HR_{L\ vs.\ T}$ 1.34, $P < 0.0005$	$HR_{T+L\ vs.\ T}$ 0.80, $P = 0.078$; $HR_{T\text{-}L\ vs.\ T}$ 0.91, $P = 0.433$; $HR_{L\ vs.\ T}$ 1.36, $P = 0.007$
NeoALTTO [76]	T2-T4	T	149	$T_{6\ wk}$→wP + $T_{12\ wk}$→Surg→FECx3→$T_{34\ wk}$	3.8	37	23	3-y 76%	3-y 90%
		L	154	$L_{6\ wk}$→wP + $L_{12\ wk}$→Surg→FECx3→$L_{34\ wk}$		38	18	3-y 78%	3-y 93%
		T + L	152	T + $L_{6\ wk}$→wP + T + $L_{12\ wk}$→Surg→FECx3 →T + $L_{34\ wk}$		30	13	3-y 84% $HR_{L\ vs.\ T}$ 1.06, $P = 0.81$; $HR_{T+L\ vs.\ T}$ 0.78, $P = 0.33$	3-y 95% $HR_{L\ vs.\ T}$ 0.86, $P = 0.65$; $HR_{T+L\ vs.\ T}$ 0.62, $P = 0.19$
NeoSphere [83]	Stage II or III, T > 2 cm	D + T	107	Dx4 + $T_{12\ wk}$ → Surg → FECx3 + $T_{39\ wk}$	5	19	N.A.	5-y 81%	N.A.
		D + T + P	107	Dx4 + T + $P_{12\ wk}$ → Surg → FECx3 + $T_{39\ wk}$		17	N.A.	5-y 86%	N.A.
		T + P	107	T + $P_{12\ wk}$ → Surg → Dx4 → FECx3 + $T_{39\ wk}$		27	N.A.	5-y 73%	N.A.
		D + P	96	Dx4 + $P_{12\ wk}$ → Surg → FECx3 + $T_{39\ wk}$		24	N.A.	5-y 73% $HR_{DTP\ vs.\ DT}$ 0.69 (95% CI, 0.34–1.40); $HR_{TP\ vs.\ DT}$ 1.25 (95% CI, 0.68–2.30); $HR_{DP\ vs.\ DTP}$ 2.05 (95% CI, 1.07–3.93)	N.A.

CI, confidence interval, DFS: disease-free survival; EFS: event-free survival; PFS: progression-free survival; T: trastuzumab; HR: hazard ratio; N: neratinib; N.A., not available; L: lapatinib; wP: weekly paclitaxel; Surg: surgery; FEC; fluorouracil, epirubicin, cyclophosphamide; P: pertuzumab; D: docetaxel.

Table 3
Randomized trials evaluating lapatinib, neratinib, pertuzumab, or trastuzumab emtansine as neoadjuvant treatments of HER2-posive breast cancer.

Study	Target group	Groups	No. of patients	Neoadjuvant regimens	Duration of HER2-targeted therapy (weeks)	pCR (breast) (%)	pCR (breast & axilla) (%)
GeparQuinto [65]	cN+, higher risk cN0 (ER/PgR-, and cT ⩾ 2 cm)	T	307	ECx4 + T → Dx4 + T	24	34.2	30.3
		L	308	ECx4 + L → Dx4 + L		26.0	22.7
						OR 0.68, $P = 0.03$	OR 0.68, $P = 0.04$
NSABP B-41 [66]	cT2–T3, N0–N2a	T	181	ACx4 → wPx4 + T	17	52.5	49.4
		L	174	ACx4 → wPx4 + L	17	53.2	47.4
		T + L	174	ACx4 → wPx4 + T + L	18	62.0	60.2
						$P_{T\ vs.\ T+L} = 0.095$	$P_{T\ vs.\ T+L} = 0.056$
NeoALTTO [67]	cT2-4	T	149	$T_{6\ wk}$ → wP + $T_{12\ wk}$	18	29.5	27.6
		L	154	$L_{6\ wk}$ → wP + $L_{12\ wk}$		24.7	20.0
		T + L	152	T + $L_{6\ wk}$ → wP + T + $L_{12\ wk}$		51.3	46.8
						$OR_{T\ vs.\ T+L} = 2.6$, $P_{T\ vs.\ T+L} = 0.0001$	$OR_{T\ vs.\ T+L} = 2.4$, $P_{T\ vs.\ T+L} = 0.0007$
CALGB 40,601 [68]	Stage II or III	T	120	wP + T_{16wk}	16	46	N.A.
		L	67	wP + $L_{16\ wk}$	16	32	N.A.
		L + T	118	wP + T + $L_{16\ wk}$	16	56	N.A.
						$P_{T\ vs.\ T+L} = 0.13$	
TRIO-US [69]	Stage I (cT ⩾ 1 cm), II, or III	T	34	$T_{3\ wk}$ → DCbx6 + $T_{18\ wk}$	21	N.A.	47
		L	36	$L_{3\ wk}$ → DCbx6 + $L_{18\ wk}$	21	N.A.	25
		T + L	58	T + $L_{3\ wk}$ → DCbx6 + T + $L_{18\ wk}$	21	N.A.	52
							$P_{T\ vs.\ T+L=}$ 0.45
EORTC 10,054 [70]	Stage cT2–T4	T	53	Dx3 + T → FECx3 + T	18	52	52
		L	23	Dx3 + L → FECx3 + L	18	46	36
		T + L	52	Dx3 + T + L → FECx3 + T + L	18	60	56
CHER-LOB [71]	Stage II–IIIA	T	36	$wP_{12\ wk}$ + T → FECx4 + T	26	N.A.	25.0
		L	39	$wP_{12\ wk}$ + L → FECx4 + L	26	N.A.	26.3
		T + L	46	$wP_{12\ wk}$ + T + L → FECx4 + T + L	26	N.A.	46.7
							$P = 0.019$
GEICAM 2006–14 [72]	Stage I–III	T	50	ECx4 → Dx4 + T	24	52.1	47.9
		L	52	ECx4 → Dx4 + L	24	25.5	23.5
						$P = 0.007$	$P = 0.011$
Holmes et al. [73]	Stage II–III	T	33	$T_{2\ wk}$ → FECx4 + T → $wP_{12\ wk}$ + T	⩾26	54	N.A.
		L	34	$L_{2\ wk}$ → FECx4 + L → $wP_{12\ wk}$ + L	⩾26	45	N.A.
		T + L	33	T + $L_{2\ wk}$ → FECx4 + T + L → wP_{12wk} + T + L	⩾26	74	N.A.
NSABP FB-7 [81]	Stage IIB–III	T	42	wP + $T_{16\ wks}$ → ACx4	16	N.A.	38.1
		N	42	wP + $N_{16\ wks}$ → ACx4	16	N.A.	33.3
		N + T	42	wP + T + $N_{16\ wks}$ → ACx4	16	N.A.	50.0
I-SPY 2 [80]	Stage II or III	T	22	wP + $T_{12\ wks}$ → ACx4	12	N.A.	23
		N	65	wP + $N_{12\ wks}$ → ACx4	12	N.A.	39
NeoSphere [82]	Stage II or III, T > 2 cm	D + T	107	Dx4 + T	12	29.0	21.5
		D + T + P	107	Dx4 + T + P	12	45.8	39.3
		T + P	107	T + P	12	16.8	11.2
		D + P	96	Dx4 + P	12	24.0	17.7
						$P_{T\ vs.\ T+P} = 0.014$	
TRYPHAENA [84]	Stage II or III	FEC-D	73	FEC + T + P × 3 → D + T + P × 3	18	61.6	50.7%
		D	75	FEC × 3 → D + T + P × 3	18	57.3	45.3%
		DCb	77	D + Cb + T + P × 6	18	66.2	51.9%
KRISTINE [90]	Stage II or III	DCb + T	221	DCb + Tx6	18	N.A.	55.7%
		T-DM1 + P	223	T-DM1 + Px6	18	N.A.	44.4%
							$P = 0.016$

HR: hormone receptor; pCR: pathological complete response; PgR: progesterone receptor; T: trastuzumab; L: lapatinib; EC: epirubicin and cyclophosphamide; D: docetaxel; OR: odds ratio; NSABP: National Surgical Adjuvant Breast and Bowel Project; AC: doxorubicin and cyclophosphamide: wP: weekly paclitaxel; CALGB: Cancer and Leukemia Group B; Cb: carboplatin; N.A.: not available; FEC: fluorouracil, epirubicin, and cyclophosphamide; N: neratinib; P: pertuzumab; T-DM1: trastuzumab emtansine.

[58], whereas in the second-line addition of pertuzumab to capecitabine plus trastuzumab did not improve significantly PFS as compared to trastuzumab plus capecitabine in the randomized PHEREXA trial [59]. Several recent systematic [51,60–63] and other [64] reviews have discussed HER2-targeted neoadjuvant treatments for early breast cancer.

Lapatinib

Lapatinib, an inhibitor of the HER1 and HER2 tyrosine kinases, has been compared to trastuzumab in at least 9 randomized trials as neoadjuvant treatment of HER2-positive breast cancer, 7 of which evaluated also dual HER2 inhibition with lapatinib plus trastuzumab (Table 3). Three of the trials were large with over 400 participating patients [65–67]. Chemotherapy consisted of a taxane and an anthracycline except for the NeoALTTO and the Cancer and Leukemia Group B (CALGB) 40,601 trials, where weekly paclitaxel was given, and the TRIO-US trial that evaluated the combination of docetaxel and carboplatin [65–73]. The lapatinib dose was reduced in several of the trials during the course of the study due to toxicity, notably diarrhea. The pCR rates achieved with the lapatinib regimens were similar or smaller than those achieved with the trastuzumab regimens, whereas the combination of lapatinib plus trastuzumab with chemotherapy resulted in numerically higher pCR rates as compared to trastuzumab plus chemotherapy in all 7 studies where dual HER2 inhibition was studied. Yet, the difference in the pCR rates in favor of the dual HER2 inhibition was statistically significant only in the NeoALTTO and the CHERLOB trials, where the proportion of patients who achieved pCR in the breast and/or the axilla was approximately 20% higher with lapatinib plus trastuzumab than with trastuzumab alone.

These consistently favorable pCR rates achieved with the lapatinib plus trastuzumab combination predict that such dual inhibition of HER2 improves survival outcomes in the adjuvant setting. To test this hypothesis, 8381 patients from 945 sites were randomly assigned between June 2007 and July 2011 to one of the 4 arms of the ALTTO trial, either trastuzumab alone, trastuzumab plus concomitant lapatinib, sequential trastuzumab and lapatinib, or lapatinib alone [74]. The overall duration of each HER2-targeted therapy was 12 months. The chemotherapy component varied, and the HER2-targeted therapy was given either after all chemotherapy, concomitantly with taxane therapy that followed anthracycline-containing chemotherapy, or concomitantly with docetaxel plus carboplatin (Table 2). The lapatinib only-group was closed early due to futility to detect noninferiority of lapatinib to trastuzumab, and the patients in this group were offered trastuzumab. In an analysis performed after a median follow-up time of 4.5 years, the patients who received trastuzumab plus lapatinib had a smaller hazard for breast cancer recurrence or death than those treated with trastuzumab alone, but the 97.5% confidence interval crossed one (HR 0.84, 97.5% CI 0.70–1.02) and the *P* value of 0.048 was not significant at set significance level of 0.025. The patients assigned to receive sequential trastuzumab and lapatinib had similar DFS as those assigned to trastuzumab. There was no significant difference in OS between the groups, except that the patients assigned to lapatinib alone had inferior OS. Cardiac toxicity was low irrespective the type of HER2 inhibition. The patients treated with lapatinib had more diarrhea, hepatic toxicity, and skin rash than those treated with trastuzumab. Curiously, patients who developed skin rash within 6 weeks of lapatinib initiation derived most benefit from lapatinib-based therapy [75].

A much smaller NeoALTTO trial also evaluated survival of patients randomly allocated to receive trastuzumab, lapatinib, or their combination for 1 year (Table 2) [76]. The study was not powered for this purpose, as event-free survival (EFS) and OS were secondary endpoints. The patients treated with lapatinib plus trastuzumab tended to have the best EFS, but the EFS or OS comparisons with the trastuzumab group were not significant. In the NeoALTTO patient population the patients assigned to lapatinib had similar survival as those assigned to trastuzumab.

Taken together, lapatinib may not be as effective as trastuzumab in the adjuvant or neoadjuvant treatment of early HER2-positive breast cancer, in accordance with the efficacy comparisons done in the advanced breast cancer setting [77,78]. The reasons remain speculative, but the capability of trastuzumab to elicit ADCC could be important [79]. On the other hand, dual HER2 inhibition with trastuzumab plus lapatinib appears slightly more effective than trastuzumab alone, but no significant advantage in DFS or OS has been demonstrated, and the combination is associated with greater toxicity and cost. Even relatively mild non-hematological toxicity, such as diarrhea, might influence compliance in the adjuvant setting due to its long duration. The currently available data suggest that the combination of adjuvant trastuzumab plus lapatinib cannot be recommended as the standard of care for patients with early HER2-positive breast cancer [74].

Neratinib

Two randomized trials, NSABP FB-7 and I-SPY 2, compared neratinib to trastuzumab in combination with weekly paclitaxel, each followed by 4 cycles of AC, as neoadjuvant treatment of early HER2-positive breast cancer (Table 3). The neratinib-containing regimen graduated as likely more effective compared with the trastuzumab-containing regimen in the I-SPY 2 trial in the subset of patients with HER2-positive, hormone receptor-negative cancer [80]. On the other hand, in the FB-7 trial the trastuzumab regimen was numerically slightly more effective in this subgroup of patients [81]. In each trial the number of patients with HER2-positive, hormone receptor-negative cancer was small. The combination of neratinib, trastuzumab, and paclitaxel was also evaluated in the FB-7 trial resulting in a higher pCR rate (50.0%) as compared with the trastuzumab or neratinib regimens (38.1% and 33.3%, respectively) in the entire patient population with HER2-positive cancer [81].

Pertuzumab

Pertuzumab is the first drug approved based on pCR as the endpoint. It was approved for the neoadjuvant treatment of HER2-positive breast cancer mostly based on the findings in the NeoSphere trial that accrued 417 patients from 59 centers from December 2007 to December 2009 [82]. NeoSphere compares 4 regimens, docetaxel plus concomitant trastuzumab, docetaxel plus trastuzumab and pertuzumab, trastuzumab plus pertuzumab (without docetaxel), and docetaxel plus pertuzumab. A higher pCR rate in the breast was obtained with the combination of docetaxel, trastuzumab, and pertuzumab than with docetaxel plus trastuzumab (45.8% and 29.0%, respectively; $P = 0.014$; Table 3). The trastuzumab plus pertuzumab and the docetaxel plus pertuzumab combinations yielded somewhat lower pCR rates.

The patients in each group were treated with trastuzumab after surgery to complete 12 months of HER2-targeted therapy (Table 2). After a median follow-up time of 5 years progression-free survival (PFS) tended to be higher in the docetaxel plus trastuzumab plus pertuzumab group as compared with the docetaxel plus trastuzumab group (HR 0.69, 95% CI 0.34–1.40). Patients treated with docetaxel and pertuzumab had less favorable PFS. OS results were not reported [83]. Pertuzumab plus trastuzumab without docetaxel was associated with the least side-effects, the most common one being grade 1–2 diarrhea (28%) [82]. Little cardiac toxicity was recorded in NeoSphere, which is in agreement with the findings in the TRYPHAENA study, where trastuzumab plus pertuzumab

was evaluated with 3 different chemotherapy backbones for cardiac toxicity (Table 3) [84].

Despite the absence of statistically significant PFS improvement in the NeoSphere patient population, the overall results are encouraging for the triple combination docetaxel, trastuzumab, and pertuzumab, as this combination improved substantially the pCR rate and was relatively well tolerated. This combination was effective also in the treatment of advanced HER2-positive breast cancer [58]. Therefore, the results of the APHINITY trial (NCT01358877) that compares chemotherapy plus trastuzumab plus pertuzumab to chemotherapy plus trastuzumab plus placebo as adjuvant treatments of early HER2-positive breast cancer are awaited with interest. APHINITY accrued 4800 patients between October 2011 and August 2013, and the first results are expected in the near future.

Afatinib

Afatinib is an irreversible inhibitor of the ERBB2 family of tyrosine kinases [85]. In the non-randomized, neoadjuvant DAFNE trial, afatinib (20 mg/d) was administered together with trastuzumab and weekly paclitaxel, followed by epirubicin, cyclophosphamide, and trastuzumab [86]. Of the 65 patients treated, 49% achieved pCR in the breast and the axilla. The most frequent nonhematologic grade 3–4 adverse effects included diarrhea (8%) and infection (5%), 1 patient had congestive heart failure. A randomized study comparing afatinib to lapatinib and to trastuzumab as neoadjuvant agents was stopped early due to slow enrollment [87].

Ado-trastuzumab emtansine (T-DM1)

T-DM1 is an antibody drug conjugate where the microtubule toxin emtansine is linked with trastuzumab. After binding to HER2 the conjugate is internalized and the payload (emtansine) is released within the cell, resulting in cell death. T-DM1 was effective in the treatment of advanced HER2-positive breast cancer in patient population refractory to trastuzumab and had a favorable safety profile [88,89].

In the KRISTINE trial (NCT02131064) 444 patients were randomly assigned to receive 6 cycles of T-DM1 plus pertuzumab or TCH (Table 3). While the pCR rate favored TCH (56% vs. 44%; $P = 0.016$), grade $\geqslant 3$ adverse events where substantially less frequent in the T-DM1 plus pertuzumab arm (13% vs. 64%) [90].

The KAITLIN trial (NCT01966471) compares adjuvant T-DM1 plus pertuzumab to trastuzumab, pertuzumab, and a taxane (weekly paclitaxel or docetaxel), each given after anthracyclines, as treatments for node-positive or high-risk node-negative HER2-positive breast cancer. KAITLIN is fully recruited with 1846 patients entered. The KATHERINE trial (NCT01772472) compares T-DM1 to trastuzumab as adjuvant treatments of patients with HER2-positive breast cancer with residual disease after neoadjuvant therapy. The duration of HER2-targeted therapy is 12 months in these trials. No results are yet available.

Concluding remarks

Despite no significant survival advantage in favor of the trastuzumab plus lapatinib combination was found in ALTTO, dual inhibition of HER2 remains a promising strategy. The discovery of novel, synergistic, and well-tolerated drug combinations is an important goal [80], and may be more important than the chase for the optimal duration of administration of single HER2-targeting agents in the adjuvant setting. Highly effective combination regimens may allow also a short duration of administration. For example, a brief duration of the docetaxel, trastuzumab, plus pertuzumab combination is being compared with chemotherapy plus 12-months of trastuzumab in the BOLD-1 trial (NCT02625441). Both the escalation and de-escalation trials being conducted are likely important for the optimization of HER2-targeted adjuvant treatments. Several of such trials will report the first results in the near future, and may modify the current standard treatment of the patients with HER2-positive early breast cancer.

Conflict of interest disclosure

Dr. Joensuu has received honoraria from consultation from Orion Pharma, BluePrint Medicines, and Ariad Pharmaceuticals. Dr. Joensuu has stock ownership in Orion Pharma, Faron Pharmaceuticals, and Sartar Therapeutics.

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