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Early HER2-Positive Breast Cancer: Current Treatment and Novel Approaches

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Abstract
Background: Trastuzumab significantly improves outcomes in early HER2-positive breast cancer, irrespectively of any prognostic or predictive factors. Unfortunately, about a quarter of patients receiving neoadjuvant trastuzumab experience disease recurrence, revealing the unquestionable need for further improvement of treatment outcomes. ***Summary:*** Adding HER2 blockade to adjuvant trastuzumab with pertuzumab and neratinib improves invasive disease-free survival (IDFS), particularly for those at highest risk of recurrence. A shift toward a neoadjuvant strategy for patients with a higher risk of recurrence could result in further treatment optimization. For patients without a pathological complete response (pCR) after the neoadjuvant part of the therapy, a switch to adjuvant trastuzumab emtansine significantly improves IDFS and distant recurrence-free survival and shows a trend towards improved overall survival (OS). On the other hand, for low-risk patients, chemotherapy de-escalation should be strongly considered with the use of trastuzumab monotherapy as an anti-HER2 backbone. ***Key Messages:*** Neoadjuvant therapy should be offered for a significant proportion of HER2-positive early breast cancer patients with a higher risk of recurrence. Postneoadjuvant treatment should be tailored according to the initial stage of disease and the response to neoadjuvant treatment.

Introduction

Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 15–20% of breast cancers and portends an aggressive phenotype and poor patient outcomes [1]. The introduction of HER2-targeted therapies has dramatically changed the prognosis for these patients. The addition of trastuzumab, a humanized monoclonal antibody that binds to the extracellular domain of HER2 receptors, to chemotherapy significantly improved survival in patients with metastatic and early-stage HER2-positive breast cancer [2]. Despite the improvement in both disease-free survival (DFS) and overall survival (OS) associated with the addition of trastuzumab to chemotherapy in early HER2-positive breast cancer, long-term follow-up data indicate that approximately 1 quarter of patients still develop disease recurrence [3]. Thus, the focus has been placed on escalating treatment by either combining different HER2-targeted agents or extending the duration of HER2-targeted therapy. In addition to trastuzumab, anti-HER2 drugs that are currently used in early breast cancer treatment include pertuzumab, a monoclonal antibody that blocks another extracellular subdomain of the HER2 receptor, the antibody-drug conjugate trastuzumab-emtansine (T-DM1), and the irreversible pan-HER2 inhibitor neratinib.

However, some patients do not derive sufficient benefit from these additional therapies to overcome the associated toxicities and/or costs. Similarly, the universal use of chemotherapy might not benefit all patients, and

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treatment deescalation through omission or deescalation of chemotherapy has shown promise in clinical trials and is currently being explored further [4].

In this article, the current standard of treatment for early HER2-positive breast cancer, treatment escalation, treatment deescalation and neoadjuvant/adjuvant treatment approaches, and novel approaches with afatinib and neratinib will be discussed.

Neoadjuvant Treatment

In the past, neoadjuvant treatment was reserved for inoperable, locally advanced, or inflammatory breast cancer in order to improve the rate and quality of surgery [4]. Since that time, the paradigm of neoadjuvant treatment has been changed, and treatment decisions currently include tumor biology in addition to tumor stage. In the context of operable disease, most patients with HER2-positive tumors that measure >2 cm and/or lymph node-positive disease receive neoadjuvant treatment [4]. The neoadjuvant concept allows in vivo testing of treatment sensitivity and further personalization of the adjuvant part of therapy and provides a way to receive accelerated approval of new therapies. It is also a valid model for the development of predictive biomarkers and the reduction of patient numbers in clinical trials [5]. The current standard of neoadjuvant therapy for HER2-positive disease is an antracycline/taxane-based chemotherapy in combination with trastuzumab and pertuzumab. This is followed by breast surgery, adjuvant radiotherapy (if indicated), completion of the HER2-directed therapy and, depending on the tumor biology, endocrine therapy.

In HER2-positive breast cancer, pCR rates of 60% or more can be achieved [6]. Different chemotherapy schedules and HER2-targeted agents, such as trastuzumab, lapatinib, pertuzumab, and T-DM1, have been investigated in the neoadjuvant setting. To achieve a higher rate of pathological complete response (pCR) and, consequently, better long-term outcomes, 2 main strategies were explored: horizontal blockade with anti-HER2-directed antibodies (pertuzumab and trastuzumab) and antibody-cytostatic conjugate (T-DM1) and vertical blockade with tyrosine-kinase inhibitor (lapatinib).

Horizontal Inhibition of the HER2 Pathway

The first randomized trial investigating neoadjuvant trastuzumab in addition to chemotherapy (NOAH trial) showed a statistically significant improvement in total pCR (38 vs. 19%; $p = 0.001$), a 5-year event-free survival (EFS) of 58 vs. 43% (HR = 0.64; 95% CI 0.44–0.93; $p = 0.016$), and a nonsignificant improvement in OS (74 vs. 63%; HR = 0.66; $p = 0.055$) [7]. Similarly, in the GeparQuattro study (epirubicin/cyclophosphamide [EC] followed by docetaxel ± capecitabine in combination with or without trastuzumab), the pCR rate was 31.7% with trastuzumab and 15.7% in the reference group [8]. After showing a significant impact on outcomes in a metastatic setting, logically, pertuzumab has been investigated in the neoadjuvant environment [9, 10].

The NeoSphere trial first showed that dual horizontal blockade with pertuzumab and trastuzumab in combination with chemotherapy resulted in a significantly improved pCR rate in the breast in comparison with trastuzumab/chemotherapy combination (pCR: 46 vs. 29%; $p = 0.0141$) without additional cardiotoxicity [10]. In the 5-year follow-up data, patients who achieved pCR had a longer progression-free survival (PFS) compared to patients who did not (i.e., 85% in patients with pCR vs. 76% in patients without pCR; HR = 0.54; 95% CI 0.29–1.00; $p = 0.0141$) [10].

The TRYPHAENA trial was designed to evaluate cardiac safety in patients treated with neoadjuvant antracycline-containing and antracycline-free chemotherapy regimens with trastuzumab and pertuzumab [9]. The combination of anti-HER2 antibodies was generally well tolerated, regardless of whether it was given sequentially or concomitantly with anthracycline-based or combined with carboplatin-based chemotherapy. The rate of achieved pCR ranges from 57.3 to 66.2% (Table 1).

After finding a significant impact on HER2-positive metastatic breast cancer outcomes, it was logical to test the value of T-DM1 in neoadjuvant treatment. Unfortunately, the place for neoadjuvant T-DM1 use is still not clearly defined.

Vertical Inhibition of the HER2 Pathway

With a vision to further improve the results obtained with trastuzumab administration in a neoadjuvant setting, lapatinib was investigated. It was hypothesized that targeting the HER2 pathway from 2 different mechanisms at the same time might improve the response rate and pCR (Table 2). The trials indicated that lapatinib was inferior to trastuzumab in the rate of pCR and that it was associated with a greater toxicity [14]. Dual HER2 blockade with the trastuzumab/lapatinib combination produced significant improvement in pCR, but unfortunately it did not translate to a significant EFS improvement [14]. In a meta-analysis, in patients receiving a combination of lapatinib and trastuzumab in comparison to trastuzumab only combined with chemotherapy, the absolute improvement in the pCR rate was 13% [14].

Newer tyrosine kinase irreversible inhibitors of different HER receptors, such as afatinib and neratinib, have

Table 1. Neoadjuvant trials with a horizontal HER2 pathway blockade strategy

Trial	Treatment arms	Rate of pCR (breast and/or nodes), %	p value	EFS/PFS, %	OS/DFS, %
Combination with trastuzumab and pertuzumab					
NEOSPHERE [7, 10]	Docetaxel/trastuzumab	29 (breast)		PFS (5 years)	DFS (5 years)
(*n* = 417; phase 2)				81	81
	Docetaxel/pertuzumab/trastuzumab	45.8	0.0141	86	84
	Pertuzumab/trastuzumab	24		73	80
	Docetaxel/pertuzumab	16.8		73	75
ADAPT (hormone receptor negative) [11]	Trastuzumab/pertuzumab/paclitaxel	90.5		NA	NA
(*n* = 134; phase 2/3)	Pertuzumab/trastuzumab	34.4			
TRYPHAENA [9]	Pertuzumab/trastuzumab/FEC followed by	61.6 (breast)		87	NA
(*n* = 225; phase 2)	docetaxel/pertuzumab/trastuzumab				
	FEC followed by docetaxel/pertuzumab/trastuzumab	57.3		88	
	Docetaxel/carboplatin/trastuzumab/pertuzumab	66.2		89	
Combination with T-DM1					
KRISTINE [12]	T-DM1/pertuzumab	44.4	0.0155	3-year EFS: HR = 2.61; 95% CI 1.36–4.98 3-year IDFS: HR = 1.11; 95% CI 0.52–2.40	NA
(*n* = 432; phase 3)					
	Paclitaxel/carboplatin/trastuzumab/pertuzumab	55.7			
I-SPY2 [13]	T-DM1/pertuzumab	52		NA	NA
(*n* = 248; phase 2/3)	Docetaxel/trastuzumab	22		NA	NA
ADAPT (HR positive)	T-DM1	41		NA	NA
[11]	T-DM1 + endocrine therapy	41.5			
(*n* = 359; phase 2/3)	Trastuzumab + endocrine therapy	15.1			

been tested in the neoadjuvant setting with results similar to those achieved with lapatinib. In the DAFNE trial patients received a combination of paclitaxel, trastuzumab, and afatinib followed by an EC. The rate of pCR was 49.2% (95% CI 38.5–60.1) [24].

Neratinib entered the neoadjuvant setting with the I-SPY2 study by the addition of HER2 status to the risk estimation according to gene profiling [26]. In the NSABP FB-7 trial, which investigated neratinib and/or trastuzumab followed by doxorubicin/cyclophosphamide, the pCR rates were 38% for trastuzumab, 33% for neratinib, and 50% in the combination arm [25].

pCR as the Primary Endpoint in Neoadjuvant Clinical Trials

The pCR rate at the time of surgery is associated with a better prognosis and provides information regarding the responsiveness of the tumor to systemic therapy. A pooled analysis defined pCR as the strongest discriminator of long-term outcomes for patients in the neoadjuvant setting [27]. Collaborative trials in neoadjuvant breast cancer (CTNeoBC) performed a meta-analysis including 12 neoadjuvant trials with 11,955 patients and follow-up of 3 years and evaluated pCR as a surrogate marker for long-term outcomes [28]. Of all breast cancer subtypes, pCR was associated with EFS (HR = 0.48; 95% CI 0.43–0.54) and OS (HR = 0.36; 95% CI 0.31–0.42). The highest pCR rates were reported in triple-negative breast cancer and HER2-positive breast cancer. Additionally, the response to neoadjuvant treatment in HER2-positive disease is dependent on the hormone receptor status. A pCR rate of 30.9% was observed in patients with HER2-positive hormone receptor-positive breast cancer with trastuzumab therapy versus 18.3% without trastuzumab (HR = 0.58; 95% CI 0.42–0.829) and 50.3% in HER2-positive hormone receptor-negative breast cancer with trastuzumab versus 30.2% without neoadjuvant trastuzumab (HR = 0.25; 95% CI 0.18–0.34). Overall, patients with pCR had a longer EFS (HER2 positive: HR = 0.39; 95% CI 0.31–0.50) and OS (HER2 positive: HR = 0.36; 95% CI 0.31–0.42).

Table 2. Neoadjuvant trials with vertical blockade of the HER2 pathway

Trial	Treatment arms	Rate of pCR (breast and/or nodes), %	*p* value	EFS/PFS/DFS, %	OS, %
GeparQuinto [15] (phase 3, *n* = 620)	EC/trastuzumab followed by docetaxel/trastuzumab	30.3	0.04	84.8	91.7
	EC/lapatinib followed by docetaxel/lapatinib	22.7		83.7	93.6
NeoALLTO [16, 17] (phase 3, *n* = 455)	Trastuzumab followed by trastuzumab/paclitaxel	29.5		EFS (3 years) 76	90 (3 years)
	Lapatinib followed by lapatinib/paclitaxel	24.7		78	93
	Trastuzumab/lapatinib followed by trastuzumab/lapatinib/paclitaxel	51.3	0.0001 (combination vs. monotherapy)	84 (ns)	95 (ns)
CHER-LOB [18, 19] (phase 2, *n* = 121)	Trastuzumab/paclitaxel followed by FEC/trastuzumab	25		77.8 (ns)	OS pCR vs. no pCR:
	Lapatinib/paclitaxel followed by FEC/lapatinib	26.3		78.1	97.2 vs. 80
	Trastuzumab/lapatinib/paklitaxel followed by FEC/trastuzumab/lapatinib	46.7	0.19 (combination vs. monotherapy)	85.8	(*p* = 0.028, 95% CI 0.02–1.08)
NSABP-B-41 [20, 21] (phase 3, *n* = 529)	AC followed by trastuzumab/paclitaxel	52.5 (breast)		84.3	94.5
	AC followed by lapatinib/paclitaxel	53.2	0.9852	78.6	89.4
	AC followed by trastuzumab/lapatinib/paclitaxel	62	0.095	90	95.7
CALBG 40601 [22, 23] (phase 3, *n* = 305)	Trastuzumab/paclitaxel	46 (breast)	0.13	Significantly longer IDFS in the trastuzumab/lapatinib/paclitaxel arm (HR = 0.34; 95% CI 0.19–0.81; *p* = 0.01)	NA
	Lapatinib/paclitaxel	32			
	Trastuzumab/lapatinib/paclitaxel	56	0.11		
DAFNE [23, 24] (phase 2, *n* = 65)	6 weeks of afatinib + trastuzumab followed by 12 weeks of paclitaxel, trastuzumab, and afatinib followed by 4 cycles EC	49.2	NA	NA	NA
NSABP FB-7 [25] (phase 2, *n* = 126)	Neratinib + paclitaxel followed by AC	33	ns	NA	NA
	Trastuzumab + paclitaxel followed by AC	38			
	Trastuzumab + neratinib + paclitaxel followed by AC	50			

NA, not available.

Adjuvant Treatment

The addition of trastuzumab to adjuvant chemotherapy reduces the risk of recurrence by approximately 40% and the risk of death by up to 30% [29–32]. According to pivotal trials and meta-analysis, the benefits of trastuzumab are independent of age, T and N stage, and hormone receptor status [31]. Importantly, real-word data confirmed a similar benefit [33]. Despite the significant impact on outcomes of trastuzumab introduction in the adjuvant setting, after a follow-up of 8–11 years, 15–24% of patients experienced disease recurrence [31]. To diminish the risk of recurrence further, many efforts have been made. One approach is extending the duration of anti-HER2 therapy (Table 3). For now, 2 strategies have been tested, i.e., trastuzumab for 2 years (HERA trial) and the sequential use of neratinib (irreversible pan-HER tyrosine kinase inhibitor) after trastuzumab (ExteNET trial) [29, 34].

Among the pivotal trials, only the HERA trial evaluated 2 years of trastuzumab. At a median follow-up of 11 years, there was no additional benefit from the prolonged HER 2 blockade [3]. As expected, the rate of cardiac toxicity was higher in the 2-year arm (7.3 vs. 4.4%) [3]. Following failure to improve outcomes and considering the increased toxicity as well as negative financial impacts, 2 years of adjuvant trastuzumab is not recommended.

Another treatment concept was evaluated in the ExteNET trial [34]. HER2-positive and disease-free patients after adjuvant chemotherapy and 1 year of trastuzumab were randomized to receiving neratinib or placebo for another year. After a 5-year follow-up, the invasive DFS was 90.2 versus 87.7% (HR = 0.73; 95% CI 0.57–0.92; *p* = 0.0083), respectively. Somewhat unexpectedly, the effect

Table 3. Adjuvant treatment escalation

Trial	Treatment arms	Primary endpoint	Trial results
Extended duration of anti-HER2 therapy			
HERA [3] (phase 3, n = 5,102)	2 years of trastuzumab vs. 1 year of trastuzumab	DFS	HR = 1.02; 95% CI 0.8–1.11
ExteNET [34] (phase 3, n = 2,840)	Neratinib administered for 1 year after completion of trastuzumab and chemotherapy	IDFS	HR = 0.73; 95% CI 0.57–0.92; p = 0.0083
Dual HER2 blockade			
• Dual blockade with trastuzumab and lapatinib			
ALTTO [35] (phase 3, n = 8,381)	Chemotherapy with trastuzumab, lapatinib, trastuzumab/lapatinib, or trastuzumab and sequential lapatinib	DFS	Lapatinib/trastuzumab is not superior to trastuzumab (HR = 0.86; 95% CI 0.74–1.00) No difference was found when comparing trastuzumab followed by lapatinib to trastuzumab (HR = 0.93; 95% CI 0.81–1.08)
• Dual blockade with trastuzumab and pertuzumab			
APHINITY [38, 39] (phase 3, n = 4,804)	Chemotherapy with pertuzumab/trastuzumab vs. Chemotherapy with trastuzumab/placebo	IDFS	45-month follow up: HR = 0.81; 95% CI 0.66–1.00; p = 0.045 For node-positive patients: HR = 0.77; p = 0.019 6-year follow-up: HR = 0.72; 95% CI 0.59–0.87
Combination of anti-HER2 agents, including T-DM1			
KAITLIN [42] (phase 3, n = 1,846)	3–4 cycles of anthracycline-based chemotherapy and then randomization: TDM1/pertuzumab vs. taxane/pertuzumab/trastuzumab	IDFS	HR = 0.98; 95% CI 0.72–1.32; p = 0.8270
KATHERINE [41] (phase 3, n = 1,468)	Patients with residual disease after neoadjuvant chemotherapy and trastuzumab received 14 cycles of T-DM1 or 14 cycles of trastuzumab	IDFS	HR = 0.50; 95% CI 0.39–0.64

was greater in the hormone receptor-positive group, most likely due to the bidirectional cross-talk between estrogen receptors and HER2 receptors. For now, an additional year of anti-HER2 therapy with neratinib after 1 year of trastuzumab only as anti-HER2 therapy should be considered for high-risk hormone receptor-positive patients.

The addition of another anti-HER2 drug, such as lapatinib, to trastuzumab in a concurrent or sequential manner was tested in the ALTTO trial [35]. Patients who did not receive adjuvant trastuzumab were randomized in the TEACH trial to receiving 1 year of placebo or lapatinib [36]. Another attempt to improve the results was the addition of the anti-VEGF antibody bevacizumab to trastuzumab (BETH trial) [37]. Unfortunately, none of those 3 concepts showed a significant benefit in terms of DFS or OS improvement.

In the adjuvant setting, in the APHINITY trial, 4,800 HER2-positive breast cancer patients were randomized to receiving chemotherapy/trastuzumab and pertuzumab or chemotherapy/trastuzumab and placebo [38]. Invasive DFS, the primary endpoint of the trial, was met. The results favored the pertuzumab arm (94.1 vs. 93.2%; HR = 0.81; p = 0.045). Updated APHINITY trial results showed the continuation of a clear benefit in the 6-year invasive DFS (87.9% with pertuzumab and 83.4% with placebo; HR = 0.72; 95% CI 0.59–0.87) in node-positive patients [39]. Despite the fact that APHINITY is a positive trial, it is important to outline that the addition of pertuzumab portends only a small benefit to the overall population and a more significant benefit to high-risk, lymph node-positive patients, and it should be advised for that group of patients only.

For now, there are no clear guidelines for the use of adjuvant pertuzumab after its neoadjuvant use, especially for patients who achieved a pCR. The majority of neoadjuvant pertuzumab trials consisted of the single agent trastuzumab in the adjuvant setting. Only in the BERENICE trial did patients continue to receive a dual blockade with an adjuvant [40]. Based on the results of neoadjuvant trials with pertuzumab use as well as the APHINITY study, for now, adjuvant pertuzumab after its neoadjuvant use should be administered only to high-risk patients with positive lymph nodes.

For patients with residual disease after neoadjuvant therapy, T-DM1 should be administered, rather than pertuzumab with trastuzumab. This recommendation is

Table 4. Adjuvant treatment deescalation

Trial	Treatment arms	Primary endpoint	Results
Shorter adjuvant anti-HER2 therapy			
FinHer [46] (n = 1,010, phase 3)	3 cycles docetaxel or vinorelbine, followed in both arms by 3 cycles of FEC; HER2-positive patients were further assigned to receiving trastuzumab for 9 weeks with docetaxel or vinorelbine	RFS	HER2-positive subgroup: 89 vs. 78%; HR = 0.42; 95% CI 0.21–0.83; p = 0.01
PERSEPHONE [50] (n = 4,088, phase 3)	Chemotherapy of the physician's choice + trastuzumab for 6 vs. 12 months	2-year DFS	89.4 vs. 89.8%; HR = 1.28; 95% CI 0.93–1.24; noninferiority margin: 1.29
PHARE [48] (n = 3,380, phase 3)	Chemotherapy followed trastuzumab for 6 vs. 12 months	2-year DFS	91.1 vs. 93.8%; HR = 1.28; 95% CI 0.1.05–1.56; p = 0.39; noninferiority margin: 1.15
SOLD [47] (n = 2,174, phase 3)	Docetaxel/trastuzumab for 9 weeks followed by FEC vs. docetaxel/ trastuzumab for 9 weeks followed by FEC followed by trastuzumab for up to 1 year	5-year DFS	85.4 vs. 87.5, HR = 1.39; 2-sided 90% CI 1.12–1.72; noninferiority margin: 1.38
ShortHER [51] (n = 1,253, phase 3)	3 cycles of docetaxel + weekly trastuzumab (9 weeks) followed by FEC vs. doxorubicine/cyclophosphamide followed by thrice weekly docetaxel with trastuzumab followed by trastuzumab for up to 1 year	5-year DFS	85.4 vs. 87.5%; HR = 1.15; 95% CI 0.91–1.46; noninferiority margin: 1.29
HORG [49] (n = 481, phase 3)	Dose-dense FEC followed by dose-dense docetaxel + trastuzumab for 6 months vs. dose-dense FEC followed by dose-dense docetaxel + trastuzumab for 12 months	3-year DFS	85.4 vs. 87.5%; HR = 1.57; 95% CI 0.086–2.10; p = 0.137; noninferiority margin: 1.53
Deescalating chemotherapy/anthracycline-free chemotherapy			
APT [44] (n = 406, phase 2)	Paclitaxel (12 weeks) concurrent with trastuzumab for 1 year	3-year DFS	98.7%; in updated analyses at 7 years the DFS was 93.3%
ATEMPT [45] (n = 497, phase 2)	T-DM1 vs. paclitaxel (12 weeks) concurrent with trastuzumab for 1 year	Clinically relevant toxicity, coprimary endpoint: 3-year DFS	98.7 vs. 92.8% The study was not powered to estimate an efficacy difference

based on the KATHERINE trial results [41]. In the randomized phase 3 trial, 1,468 HER2-positive patients with residual disease after neoadjuvant taxane-containing chemotherapy and trastuzumab or dual blockade were randomized to receiving 14 cycles of trastuzumab or 14 cycles of T-DM1. T-DM1 administration improved invasive disease-free survival (IDFS) (88 vs. 77%; HR = 0.50; 95% CI 0.39–0.64). The benefit of T-DM1 compared to trastuzumab was similar, regardless of the preoperative choice of anti-HER2 therapy. The most common adverse events leading to treatment discontinuation were thrombocytopenia (4.2%), hyperbilirubinemia (2.6%), and elevation of alanine transaminase (1%).

We are witnessing continued improvement in our understanding of breast cancer tumor biology and, based on the advances in our ability to further personalize, individualized therapeutic approaches to patients with HER2-positive early breast cancer. Generally, there are 2 main trends, i.e., treatment deescalation and treatment escalation.

Conventional chemotherapy is associated with systemic toxicity, so more effective, less toxic treatments are needed. In the KAITLIN trial, patients were randomly assigned within 9 weeks of surgery to receiving 3–4 cycles of anthracycline-based chemotherapy followed by 18 cycles of T-DM1 plus pertuzumab or a combination of 12 weeks of taxane and pertuzumab and trastuzumab for up to 1 year [42]. The primary endpoint (IDFS) was not met (HR = 0.98; 95% CI 0.72–1.32; p = 0.8270).

In addition to tumor biology, tumor size might be a potential criterion to select a subpopulation of patients who might benefit from less intensive treatment. According to a retrospective analysis, even small tumors have a significant risk of recurrence (10–30%) [43]. On the other hand, the majority of pivotal trials did not include patients with tumors <2 cm in diameter [31].

Deescalation phase 2 of a non-randomized APT trial included HER2-positive tumors <3 cm without lymph node involvement [44]. Patients received 12 weeks of paclitaxel plus trastuzumab and then trastuzumab to complete 1 year. In the updated analyses at 7 years, the DFS was 93.3%, with a 97.5% recurrence-free interval. Generally, paclitaxel-trastuzumab is a preferred regimen for tumors <2 cm, although there is no phase 3 comparison of that protocol with other regimens.

In the ATEMPT trial, the adjuvant T-DM1 was tested in a similar population. In that phase 2 trial, patients with

stage 1 HER2-positive breast cancer were randomized to receiving T-DM1 or paclitaxel-trastuzumab at a 3:1 ratio [45]. The 3-year DFS was 97.7% for the T-DM1 arm and 92.8% for paclitaxel/trastuzumab, but the study was not powerful enough to estimate the efficacy difference between the 2 study arms [45]. The toxicity profile incidence was similar between the 2 groups. For now, T-DM1 is not accepted as a standard adjuvant regimen for this population.

For low-risk HER2 tumors, a shorter trastuzumab administration was tested in our attempt to decrease cardiotoxicity and lower the financial burden of anti-HER2 therapy. The oldest one was FinHER, with 9 weeks of adjuvant trastuzumab versus observation, which showed a 58% reduction of the risk of death ($p = 0.01$) [46]. In the SOLD trial, investigators compared 9 weeks versus 1 year of adjuvant trastuzumab [47]. This noninferiority trial did not show that 9 weeks was as good as 1 year (5-year DFS: 88.0 vs. 90.5%, respectively; HR = 1.39; 2-sided 90% CI 1.12–1.72). Other noninferiority trials, such as PHARE, HORG, and PERSEPHONE, compared 6 months versus 1 year of adjuvant trastuzumab treatment [48–50]. Neither the PHARE trial (HR = 1.08; 95% CI 0.93–1.25; $p = 0.39$) nor the HORG trial showed noninferiority (HR = 1.57; 95% CI 0.86–2.10; $p = 0.137$). Only the PERSEPHONE trial showed noninferiority (89.4 vs. 89.9%; HR = 1.07; 95% CI 0.93–1.24; Table 4) [50]. Cardiotoxicity was higher in frequency in the 12-month group compared with the 6-month group, although the incidence was low and reversible. A conclusion of our attempts to shorten the length of adjuvant trastuzumab use is that 1 year remains the standard and, if needed, because of toxicity or other reasons, we can stop trastuzumab early without damaging the interests of our patients significantly.

Conclusion

Trastuzumab has changed the landscape of the treatment of patients with early HER2-positive breast cancer. Introduction of a dual blockade in the neoadjuvant setting improved the rate of pCR, which translated to better long-term outcomes. The benefit of dual anti-HER2 blockade in the adjuvant setting with either pertuzumab or neratinib added to trastuzumab has shown modest improvement in DFS. Dual inhibition with trastuzumab and pertuzumab should be reserved for lymph node-positive patients only. The use of T-DM1 in patients with residual disease after neoadjuvant treatment has shown significant benefits in IDFS. For now, chemotherapy deescalation in combination with trastuzumab should be recommended for small, node-negative, HER2-positive tumors.

Despite significant improvement in HER2-positive early breast cancer treatment, there are still unanswered questions. Biologic heterogeneity within HER2-positive breast cancer requires further investigation in order to develop valid biomarkers that will lead to a better definition of different risk subgroups of patients who might benefit from different treatment strategies.

Conflict of Interest Statement

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