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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

When to Add Additional Anti-HER2 Therapy to Adjuvant Trastuzumab

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Abstract

Purpose of Review One year of trastuzumab dramatically improves outcomes in early HER2 positive breast cancer, irrespective of anatomic stage, receptor status and chemotherapy backbone. However, up to 25% of breast cancers treated with trastuzumab and chemotherapy recur. Here, we review the current role for additional HER2 blockade to adjuvant trastuzumab.

Recent Findings Adjuvant pertuzumab and neratinib modestly improve disease-free survival in early breast cancer, particularly for those at highest risk of recurrence. Lack of complete pathologic response to preoperative chemotherapy and HER2 targeted therapies is associated with worse outcomes. In those with lack of pCR, adjuvant trastuzumab emtansine improves outcome in early breast cancer, irrespective of chemotherapy and HER2 targeted therapy backbone.

Summary Preoperative chemotherapy and HER2 targeted therapy should be discussed in early breast cancer, especially in tumors over 2 cm. Future trials must focus on de-escalation of chemotherapy and biomarkers for further tailored therapy in early HER2 positive breast cancer.

Keywords HER2 · Pertuzumab · Adjuvant · Early · Neratinib · TDM1 · Trastuzumab emtansine · Neoadjuvant · Pathologic complete response

Introduction

The addition of 1 year of trastuzumab to chemotherapy for patients with early-stage HER2-positive breast cancer significantly improves long-term outcomes and that has been demonstrated by several phase III trials irrespective of anatomic stage, hormone receptor status and chemotherapy backbone. A metanalysis from eight major trials evaluating 11,991 patients that received adjuvant trastuzumab, reported improvement in disease-free survival (HR 0.66; 95% CI 0.57–0.77, $p < 0.00001$) and overall survival (HR 0.60; 95% CI 0.50–0.71, $p < 0.00001$) [1]. Patients with largely anatomic stage I disease who received the combination of 12 weeks of paclitaxel and 1 year of trastuzumab experienced excellent 93.3% DFS [2]. One year of trastuzumab is superior to six months in the vast majority of patients and is the standard of care [3]. Nevertheless, long-term follow-up data from those trials' showed that up to 15–24% of the patients will suffer some form of recurrence in 8–11 years [4–6]. The development of new agents targeting HER2 raised the question about possible increased benefit with dual or extended blockade in different settings of early stage breast cancer therapy.

Neoadjuvant Versus Adjuvant Therapy in Breast Cancer

The treatment of high-risk early breast cancer typically comprises local and systemic therapy. In the quest to improve the outcomes of breast cancer treatment, the use of chemotherapy before (neoadjuvant) or after (adjuvant) surgery has been repeatedly evaluated. For most cases, the standard has been to offer adjuvant chemotherapy. The possible advantages to neoadjuvant chemotherapy are reduction in tumor size and possible conversion of inoperable to operable tumors or improvement of cosmetic results in operable ones; and real-time information about tumor chemo sensitivity based on the response

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seen in the primary tumor. Theoretically, the neoadjuvant approach would target micrometastatic disease earlier in the treatment. In practice, no clear difference in long-term outcomes has been seen, and multiple studies have reported no difference in distant recurrence and overall survival for neoadjuvant versus adjuvant chemotherapy [7–9].

Recently, a metanalysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTG) evaluated data from ten randomized trials comparing the same chemotherapy regimens given as neoadjuvant or adjuvant therapy, to a total of 4756 women between the years 1983 and 2002, with a median follow-up of 9 years [10]. The publication confirmed no significant difference between neoadjuvant and adjuvant chemotherapy for distant recurrence (15 year risk 38·2% for neoadjuvant vs 38% for adjuvant chemotherapy (HR 1·02, 95% CI 0·92–1·14, $p = 0·66$), breast cancer mortality (34·4% vs 33·7%, HR 1·06, 95% CI 0·95–1·18, $p = 0·31$), or death from any cause (40·9% vs 41·2%; HR 1·04, 95% CI 0·94–1·15; p = 0·45). However, neoadjuvant chemotherapy was associated with increased local recurrence in comparison to adjuvant chemotherapy (15-year local recurrence 21·4% for neoadjuvant versus 15·9% for adjuvant chemotherapy (5·5% increase, 95% CI 2·4–8·6, HR 1·37, 95% CI 1·17–1·61, $p = 0·0001$); a trend also found in other studies [11, 12]. However, these data preceded routine use of HER2 targeted therapies.

More recently, the use of neoadjuvant chemotherapy has provided pathological information regarding treatment response once the surgical resection is performed, introducing a new concept and potential surrogate marker in the evaluation of breast cancer long-term outcomes, the pathological complete response (pCR). Recent data suggest that changing therapies in the adjuvant setting for those patients with no pCR and a RCB (residual cancer burden) of greater then 0, improve disease free survival [13••].

Neoadjuvant Therapy and Significance of pCR

Multiple neoadjuvant randomized trials evaluated pCR and demonstrated an association with long-term outcomes [14]. A metanalysis of 12 international neoadjuvant clinical trials with 11,955 patients and available long-term clinical data, established a definition of pCR that better correlated with long-term outcomes as absence of invasive disease in breast and lymph nodes, and reinforced the finding that the association between pCR and long-term outcomes seems to be stronger in tumor subtypes such as triple-negative and HER2-positive breast cancer.

The US Food and Drug Administration (FDA) recommended pCR as a surrogate endpoint for accelerated approval of new treatments for neoadjuvant treatment of high-risk early-stage breast cancer [15, 16]. Pertuzumab was the first drug to be approved under this new guidance [17].

Improvements in pCR have had mixed results in terms of translating to improved survival. While it is known that patients who achieve a pCR seem to have better outcomes, it is unclear what improvement in pCR rate is required to achieve a clinically significant improvement in disease free survival (DFS) and overall survival (OS) [18]. In attempts to correlate rate of pCR with long-term outcomes, uniformization of pCR reports were recommended, as well as categorization of residual cancer burden (RCB) after neoadjuvant therapy [19, 20]. In a retrospective evaluation of long-term prognostic risk after neoadjuvant chemotherapy associated with RCB and breast cancer subtype, the HER2-positive group effectively treated with trastuzumab was small (around 200 patients) but showed estimates of 10-year relapse-free survival rates in the four RCB classes (pathologic complete response, RCB-I, RCB-II, and RCB-III) of 95%, 77%, 47%, and 21% respectively. [21] Other reasons that may account for lack of robust improvements in disease free survival despite improvement in pCR may be due to different molecular subtypes and tumor heterogeneity. The most impressive benefit from HER2 targeted therapy seems to be derived by those with HER2 enriched molecular signatures [22].

The benefit of adding anti-HER2 blockage to the neoadjuvant treatment in HER2-positive breast cancer was demonstrated in the pivotal NOAH trial [23]. In this phase II trial, 235 HER2-positive breast cancer were randomized between neoadjuvant chemotherapy plus or minus trastuzumab, followed by adjuvant trastuzumab to complete a total of 1 year. Trastuzumab increased pCR rate to 38% vs 19% ($p = 0.0007$) and improved 5.4-year event-free survival rate to 58% vs 43% (HR 0.64, 95% CI 0.544–0.930, $p = 0.016$) [24].

Several agents targeting HER2 were evaluated in neoadjuvant clinical trials with pCR as a primary endpoint with dual inhibition.

Agents Evaluated in Neoadjuvant and/or Adjuvant Trials for HER2-positive Breast Cancer and Double or Extended Anti-HER Blockade

Lapatinib

Lapatinib is a small molecule dual tyrosine kinase inhibitor targeting the epidermal growth factor (EGFR or HER1) and HER2. The NeoALTTO, a phase III randomized trial, evaluated neoadjuvant combination of paclitaxel to lapatinib plus trastuzumab versus paclitaxel plus trastuzumab in 455 patients with HER-2 positive operable breast cancer. Despite significant doubling of the pCR rate (51.3% lapatinib plus trastuzumab vs 29.5% trastuzumab alone, $p = 0.0001$), it did not translate into higher survival in the combination group [25, 26]. One caveat is that all patients received further

systemic therapy after surgery. Therefore, the pCR rates in each of the arms did not affect the long-term outcome of these patients alone.

Nevertheless, NeoALTTO demonstrated that women who achieved a pCR had significantly better 3-year event-free survival (hazard ratio 0.38, $p = 0.003$ and OS hazard ratio 0.35, $p = 0.005$) than those who did not achieve a pCR. Interestingly, pCR was significantly associated with event-free survival and overall survival benefit only in the patients with hormone receptor negative tumors. To evaluate the adjuvant effect of adding lapatinib to trastuzumab versus the use of trastuzumab alone in that setting, the ALTTO trial enrolled 8381 patients, and reported that the addition of lapatinib to trastuzumab did not translate into an improvement in recurrence or survival at a median follow-up of 4.5 years [27•].

Neratinib

Neratinib is an irreversible small-molecule tyrosine kinase inhibitor of HER1, HER2, and HER4 [28]. In the I-SPY-2 trial, patients with HER2-positive breast cancer were randomized to receive neoadjuvant weekly paclitaxel with neratinib for 12 weeks or weekly paclitaxel with trastuzumab; both groups then received 4 cycles of doxorubicin and cyclophosphamide. The pCR rate with neratinib was 56% (95% CI 37%–73%) versus 33% on the trastuzumab arm (95% CI 11%–54%) in patients with a hormone receptor negative and HER2 positive signature [29].

The ExteNET trial evaluated 1 year of neratinib given to 2840 high-risk early stage HER2-positive breast cancer patients after they had completed neoadjuvant and adjuvant chemotherapy with the standard use of trastuzumab for 1 year and no evidence of disease recurrence or metastatic disease at study entry [30•]. Eligible patients were randomized to receive one year of oral neratinib versus placebo. After a median follow up of 5 years, patients in the neratinib group had significantly fewer invasive DFS (iDFS) events than those in the placebo group (116 vs 163 events) with a hazard ratio of 0.73 (95% CI 0·57–0·92, $p = 0.0083$). The 5-year iDFS was 90.2% (95% CI 88·3–91·8) in the neratinib group and 87.7% (85·7–89·4) in the placebo group, a 2.5% difference. Interestingly, exploratory analysis showed a higher iDFS benefit in the hormone-receptor positive group than the hormone-receptor negative group (HR 0.60, 95% CI 0.43–0.83 vs HR 0.95, 95% CI 0.66–1.35, $p = 0.063$); in those with involvement of four or more lymph nodes (HR 0.67, 95% CI 0.46–0.96); and in those that started neratinib within 1 year of completion of trastuzumab (HR 0.70, 95% CI 0.54–0.90). In those with ER negative disease that started neratinib within 6 months, there was a numerical 2.8% benefit that was not statistically significant [31].

The group receiving neratinib had more adverse events than the placebo group: grade 3–4 diarrhea in 40% vs 2%, grade 1–2 nausea in 41% vs 2%, and grade 1–2 vomiting 23% vs 8%, respectively. Discontinuation of treatment due to adverse events occurred in 28% patients in the neratinib group versus 5% of patients in the placebo group. The analysis of overall survival is planned for after 248 events and expected by the end of 2019.

Pertuzumab

Pertuzumab is a monoclonal antibody that targets the extracellular dimerization domain of HER2 and inhibits the ligand-dependent heterodimerization of HER2 with other family members including EGFR, HER3, and HER4. In the metastatic setting, the CLEOPATRA study demonstrated significantly improved progression-free survival from 12 months to 19 months (HR 0.62, 95% CI 0.51–0.75), and overall survival from 40.8 months to 56.5 months (HR 0.68, 95% CI 0.56–0.84) with the addition of pertuzumab to trastuzumab and docetaxel. Toxicity was increased in the pertuzumab arm, with higher rates of diarrhea, neutropenia, rash, and febrile neutropenia [32].

Two phase II trials granted pertuzumab the FDA accelerated approval for use in the neoadjuvant setting for patients with HER2-positive locally advanced, inflammatory, or early-stage (when tumor size is >2 cm in diameter or node positive) breast cancer. The NeoSphere trial enrolled 417 women who were randomized to receive 1 of 4 regimens prior to surgery: docetaxel plus trastuzumab; docetaxel plus trastuzumab and pertuzumab; trastuzumab plus pertuzumab; or docetaxel plus pertuzumab. After four cycles of treatment, patients underwent surgery and pCR rates were significantly higher when combining the three drugs, 46% versus 29%, 17%, and 24%. Following surgery, patients continued to received adjuvant trastuzumab therapy along with an anthracycline chemotherapy regimen. The NeoSphere study was not powered to detect differences in PFS [33]. The TRYPHAENA randomized 255 patients to three arms with anthracycline containing vs. non-anthacycline containing combination chemotherapy regimens to evaluate cardiac safety. The three arms consisted of: A) 5-fluorouracil, epirubicin and cyclophosphamide (FEC) with concurrent trastuzumab and pertuzumab ×3, followed by docetaxel, trastuzumab and pertuzumab (THP) × 3; B) FEC × 3 followed by THP × 3, and C) the non-anthracycline regimen of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) × 6. The study was not powered to detect differences of pCR between the arms, but reported pCR rate of 61.6% in Arm A, 57.3% in Arm B, and 66.2% in Arm C [34]. Long-term DFS and PFS were similar between the three arms (87%, 88%, and 90%; and 89%, 89%, and 87%) [35]. However, patients that achieved a pCR had superior DFS independent of the HER2 backbone. [33, 35]

Pertuzumab was granted FDA regular approval based on the confirmatory adjuvant phase III trial APHINITY, that randomized 4805 node-positive or node-negative and high-risk features (histological or nuclear grade 3, hormonal receptor negativity and age younger than 35 years) HER2-positive breast cancer patients to standard chemotherapy (including both anthracycline and non-anthracycline containing regimens per the investigators choice) plus trastuzumab with either pertuzumab or placebo for 1 year [36••]. The 3-year rate of iDFS was 94.1% in the pertuzumab group and 93.2% in the placebo group (HR 0.88, 85% CI 0.66–1.0, $p = 0.045$). 63% of the patients enrolled in the trial had lymph node involvement and 36% had hormone receptor–negative tumors. In a preplanned subgroup analysis, no treatment effect was seen in the node-negative patients while the 3-year iDFS was significantly different in the node-positive group, 92% with pertuzumab vs 90.2% with placebo (HR 0.77, 95% CI 0.62–0.96, $p = 0.02$). The tests for interaction of the treatment effect were not significant for any of the patients of groups. Toxicity profile was similar between both groups, although severe diarrhea was more frequent with pertuzumab (9.8% vs 3.7%), mainly during the concomitant chemotherapy administration period.

Trastuzumab Emtansine

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate containing emtansine (DM1), a microtubule-inhibitory agent, linked to trastuzumab. It is approved as second line therapy for metastatic HER2-positive breast cancer [37, 38].

In the neoadjuvant setting, looking specifically into the hormone-receptor positive HER2-positive breast cancer cases, in an attempt to de-escalate therapies in this subtype of breast cancer, a phase II trial evaluated 376 patients randomly assigned to receive neoadjuvant treatment with 12 weeks of T-DM1 alone, T-DM1 plus endocrine therapy or trastuzumab plus endocrine therapy [39]. The neoadjuvant treatment was then followed by surgery and adjuvant chemotherapy according to local standards. The primary endpoint of the trial was the rate of pCR. The arms containing T-DM1 achieved higher pCR rates 41% with T-DM1 alone, 41.5% with T-DM1 plus endocrine therapy, and 15.1% with trastuzumab plus endocrine therapy ($p < 0.00$). In conclusion, the addition of targeted chemotherapy was more effective in achieving pCR.

Building upon the demonstrated increase in pCR achieved by dual HER2 blockade with trastuzumab and pertuzumab, the phase III trial KRISTINE compared it to a neoadjuvant regimen that replaced systemic chemotherapy with targeted chemotherapy using T-DM1 [40]. A total of 444 high-risk early breast cancer patients were randomized to receive the combination trastuzumab plus pertuzumab with chemotherapy (docetaxel plus carboplatin [TC]) or pertuzumab combined with T-DM1 for 6 cycles. The main endpoint of the study was pCR rate, found to be 55.7% in the standard chemotherapy group vs 44.4% in the T-DM1 plus pertuzumab group (95% CI -20.5 to −2.0, $p = 0.016$). Among those randomized to the T-DM1 and pertuzumab arm, 6.7% experienced local regional progression prior to surgery attributed to HER2 heterogeneity. As expected, adverse events were more prominent in the standard chemotherapy group, with grade 3–4 events of 29% vs 5%. Among all patients who underwent surgery ($n = 418$), pCR was associated with a reduced risk of an iDFS event regardless of treatment arm or hormone receptor status (stratified HR for pCR versus residual disease, 0.24 [95% CI, 0.09 to 0.60]). In patients with a pCR, risk of an iDFS event was similar between treatment arms (stratified HR, 0.99 [95% CI, 0.20 to 4.96]). The 3-year iDFS event-free rate was similarly high in the T-DM1 plus pertuzumab arm (96.7% [95% CI, 93.0% to 100.0%]) and TC plus trastuzumab and pertuzumab arm (97.5% [95% CI, 94.7% to 100.0%]) for patients with pCR. In patients with residual disease—regardless of whether they received optional adjuvant chemotherapy—the risk of an iDFS event was also similar between treatment arms (stratified HR, 0.94 [95% CI, 0.38 to 2.33]). The 3-year iDFS event-free rate was 89.4% (95% CI, 83.1% to 95.6%) in the T-DM1 plus pertuzumab arm and 84.2% (95% CI, 72.5% to 96.0%) in the TC plus trastuzumab and pertuzumab arm for patients with residual disease [41].

Considering the higher risk of recurrence seen in HER2-positive breast cancer with residual disease after neoadjuvant anti-HER2 and chemotherapy, and the effectiveness of T-DM1 as second-line anti-HER2 therapy plus its favorable toxicity profile, the phase III KATHERINE trial was developed [13]. The interim analysis reported on 1486 patients who had residual disease in breast or axillary lymph nodes after completion of neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab. Patients were randomized to receive adjuvant T-DM1 or trastuzumab for 14 cycles. The estimated 3-year iDFS was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group (HR 0.5, 95% CI 0.39–0.64, $p < 0.001$). The benefit was consistent in all subgroup analysis across stratification cohorts, including hormone-receptor positive and negative patients. Adverse events were higher in the T-DM1 group, with grade 3–4 toxicity in 25.7% vs 15.4%, mostly related to thrombocytopenia (3.6%) and peripheral sensory neuropathy (1.4%).

Table 1 summarizes the main trials that evaluated HER2-positive breast cancer and dual or extended anti-HER blockade in the adjuvant setting. Currently, there are only two trials evaluating the addition of anti-HER2 blockade to trastuzumab with pending results. (Table 2). With the hypothesis that the dual blockade is more effective than the longer duration single blockade with trastuzumab, the BOLD-1 trial (NCT02625441) is randomizing HER2-positive breast cancer patients in Finland to receive either in an adjuvant or neoadjuvant setting, the combination of trastuzumab plus pertuzumab and chemotherapy (with anthracycline and taxane) versus trastuzumab alone and the same chemotherapy

Table 1 Major trials evaluating additional anti-HER2 agents to adjuvant trastuzumab

Phase III Trial	Treatment	Efficacy	Toxicity
ALTTO [27•] NCT00490139 **8381 patients**	Trastuzumab 52 weeks vs Trastuzumab 12 weeks - > Lapatinib 34 weeks Trastuzumab plus Lapatinib 42 weeks (after adjuvant chemotherapy)	4.5-year DFS HR 0.96; $p = .61$ HR 0.84; $p = .048$ (NS)*	Lapatinib increased Grade 3–4 diarrhea, cutaneous rash and hepatotoxicity
ExteNET [30•] NCT00878709 **2840 patients**	Neratinib 1 year vs Placebo 1 year (after chemotherapy and trastuzumab 1 year)	5-year iDFS 90.2% vs 87.7% HR 0.73; $p = .0083$	Neratinib increased Grade 3–4 diarrhea, nausea, vomiting
APHINITY [36••] NCT01358877 **4805 patients**	Trastuzumab plus Pertuzumab 1 year vs Trastuzumab plus placebo 1 year (after adjuvant chemotherapy)	3-year iDFS 94.1% vs 93.2% HR 0.88, $p = .045$	Similar toxicity profile
KATHERINE [13••] NCT01772472 **1486 patients**	Trastuzumab ×14 vs T-DM1 ×14 (non-pCR, after neoadjuvant chemotherapy)	3-year iDFS 88.3% vs 77% HR 0.5, $p < .001$	T-DM1 increased Grade 3–4 thrombocytopenia and peripheral neuropathy

DFS: disease-free survival; iDFS: invasive disease-free survival; pCR: pathological complete response

*alpha-error set at 0.25

followed by maintenance with trastuzumab to complete a total of 1 year. The other phase III trial (NCT01966471) is evaluating the adjuvant effect of anthracycline based chemotherapy followed by the combination trastuzumab, pertuzumab and taxane versus T-DM1 and pertuzumab, with both arms offering dual anti-HER2 targeting with different agents.

Practical Considerations on which Patients Should Receive Additional Anti-HER2 Therapy to Adjuvant Trastuzumab

In practice, the benefits of therapy need to be weighed against cost and toxicity when recommending escalating HER2 targeted therapy in early breast cancer. Adjuvant pertuzumab and neratinib confer modest benefits and risks/benefits are discussed in the ASCO guideline [44]. In patients with tumors over 2 cm and/or nodal involvement neoadjuvant pertuzumab should be discussed; while no data are available to inform the duration of pertuzumab therapy in patients that received neoadjuvant pertuzumab and achieved pCR, one year of pertuzumab is reasonable if there is good tolerability (Fig. 1).

Neratinib may be discussed as extended therapy in high-risk disease, or those that did not achieve a pCR. Anti-diarrheal prophylaxis is important in patients that receive neratinib [45]. Importantly, the benefit of neratinib in patients that received pertuzumab and/or T-DM1 is unknown.

The KATHERINE trial has shifted the paradigm on optimal management of HER2 positive breast cancer. Patients with tumors over 2 cm should be offered preoperative therapy.

Table 2 Ongoing trials adding adjuvant anti-HER2 agents to trastuzumab

Trial	Number patients	Register number	Treatment arms	Primary endpoint
BOLD-1 [42] Phase III	1366 (recruiting)	NCT02625441	(adjuvant or neoadjuvant) Docetaxel, trastuzumab, pertuzumab 3x - > FEC 3x vs Docetaxel, trastuzumab 3x - > FEC 3x - > trastuzumab1 year	iDFS
Phase III [43]	1846 (active, not recruiting)	NCT01966471	FAC/AC or EC - > trastuzumab, pertuzumab, taxane vs FAC/AC or EC - > T-DM1, pertuzumab	iDFS

iDFS: invasive disease-free survival

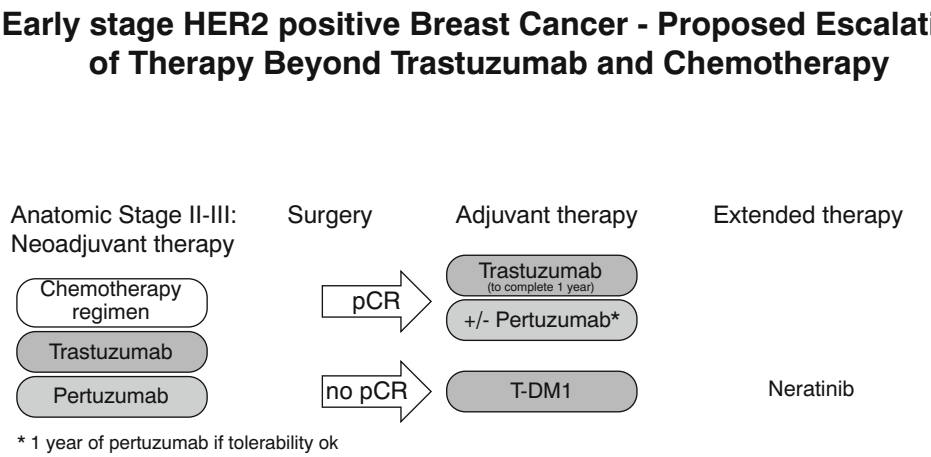

Fig. 1 Early-stage HER2-positive breast cancer: proposed escalation of therapy beyond trastuzumab and chemotherapy. *1 year of pertuzumab if tolerability ok

For patients that received neoadjuvant treatment with cytotoxic chemotherapy and HER2 targeted therapy who did not achieve a pCR, the recommendation to offer adjuvant T-DM1 for 14 cycles showed clear DFS benefit and tolerable toxicity profile.

Conclusion

Trastuzumab clearly improves outcomes in early stage HER2 positive breast cancer irrespective of stage, hormone receptor status or chemotherapy backbone. Dual HER2 targeted neoadjuvant therapy improves pCR, and those patients that achieve pCR have better outcomes than those that do not achieve a pCR. The benefit of dual anti-HER2 therapy in the adjuvant setting has been demonstrated in different degrees by clinical trials evaluating different agents in different groups of patients. The use of T-DM1 in patients with residual disease after neoadjuvant treatment has shown the greater benefit in iDFS, but final results in OS are still awaited. Escalation of therapy with pertuzumab and neratinib in the adjuvant setting has led to modest improvement in DFS, particularly in those at highest risk of recurrence. Future trials should focus on de-escalating therapy in HER2 enriched tumors, decreasing chemotherapy, and escalating therapy in those that do not achieve pCR following neoadjuvant therapy. Biomarkers of benefit for agents beyond trastuzumab are integral to further personalization of early HER2 targeted therapy.

Compliance with Ethical Standards

Conflict of Interest Alexandra S. Zimmer declares that she has no conflict of interest.

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- • Of importance
- •• Of major importance

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