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Review

Perioperative HER2 targeted treatment in early stage HER2-positive breast cancer

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***Abstract*:** Although human epidermal growth factor receptor 2 (HER2)-positive breast cancer was associated with poor prognosis, it has been changed after the development of trastuzumab. There has been great progress in perioperative HER2-targeting treatment, and investigations of several novel drugs and their combinations are ongoing. Adjuvant trastuzumab with or without pertuzumab for 1 year in combination with concomitant chemotherapy has become a standard treatment in high-risk node-negative tumors or node-positive HER2-positive early breast cancer patients without residual disease or who have not received neoadjuvant treatment. For low-risk HER2-positive early breast cancer patients, adjuvant paclitaxel and 1-year trastuzumab are possible alternatives. For residual disease after neoadjuvant treatment, adjuvant trastuzumab emtansine (T-DM1) for 14 cycles is a standard treatment. Non-anthracycline chemotherapy with dual anti-HER2 targeting of trastuzumab and pertuzumab represents one of the preferred neoadjuvant regimens to achieve higher pathologic complete response (pCR) rates and better clinical outcomes. Further research is needed to develop and validate potential biomarkers to predict pCR, which could help escalate or de-escalate anti-HER2 therapy. Trials incorporating novel agents such as T-DM1, trastuzumab deruxtecan (T-DXd), and immune checkpoint inhibitors and trying to de-escalate treatments in neoadjuvant setting are ongoing. In the future, tailored treatments such as no adjuvant therapy, various HER2-directed therapies alone with chemotherapy, combinations of various HER2-directed therapies and chemotherapy, addition of immune checkpoint inhibitors, and omission of surgery will be individualized in HER2-positive early breast cancer patients.

Keywords: adjuvant therapy, early breast cancer, HER2+ breast cancer, HER2-targeted therapy, neoadjuvant therapy

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Introduction

Human epidermal growth factor receptor 2 (HER2) is a member of the *ErbB* family of transmembrane receptor kinases, of which there is amplification or overexpression in 20–30% of invasive breast cancers. HER2 amplification and overexpression are associated with metastasis, relapse, and reduced survival.[1,2]

HER2-positive breast cancer treatment is a model of successful treatment progress based on trastuzumab. With the development of trastuzumab, there has been great progress in perioperative HER2-targeting treatment, and investigations of several novel drugs and their combinations are ongoing.

Adjuvant HER2 treatment

Adjuvant trastuzumab

Trastuzumab is a humanized monoclonal antibody targeting the extracellular domain of HER2. Either alone or in conjunction with chemotherapy, it has shown efficacy in first-line treatment of HER2-overexpressing metastatic breast cancer.[3,4] In addition to its efficacy in the metastatic setting, it has shown efficacy in adjuvant settings.[5–7] In a

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joint analysis of NSABP B-31 and NCCTG N9831, 52 weeks of adjuvant trastuzumab combined with paclitaxel following doxorubicin and cyclophosphamide improved clinical outcomes including disease-free survival (DFS) and overall survival (OS) compared to the chemotherapy-only group in surgically removed and node-positive or high-risk node-negative [tumor size greater than 2 cm if positive for estrogen or progesterone receptors or greater than 1 cm if negative for both hormone receptors (HRs)] HER2-positive breast cancer patients.[7] This benefit of additional adjuvant trastuzumab in early-stage HER2-positive breast cancer patients persisted in a subsequent analysis with median follow-up of 8.4 years.[8] In the latest meta-analysis of 13,864 patients, where the median follow-up was 10.7 years, trastuzumab in addition to chemotherapy in early-stage HER2-positive breast cancer patients consistently reduced recurrence and mortality rates.[9]

In the HERA trial, node-positive or high-risk node-negative (tumor size larger than 1 cm) HER2-positive breast cancer patients who had completed locoregional therapy and neoadjuvant or adjuvant chemotherapy were randomly assigned to trastuzumab for 2 years, trastuzumab for 1 year, or observation. Trastuzumab for 1 year significantly improved DFS compared with observation.[6] After a median follow-up of 11 years in this trial, the benefit of 1-year trastuzumab in terms of DFS persisted compared with observation. However, 2-year trastuzumab did not show additional benefit compared to 1-year trastuzumab.[10]

In contrast, sequential 1-year trastuzumab after adjuvant anthracycline-based chemotherapy with or without docetaxel in axillary node- and HER2-positive breast cancer patients was not associated with a significant increase in 3-year DFS compared to the observation group in the FNCLCC-PACS 04 trial.[11] However, DFS was significantly higher in the trastuzumab group than in the observation group in the per-protocol populations after a median follow-up of 115 months, even though OS was not different.[12]

In the BCIRG-006 trial, node-positive or high-risk node-negative HER2-positive early-stage breast cancer patients were randomly assigned to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), AC-T plus 52 weeks of trastuzumab (AC-TH), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH) for adjuvant treatment.[13] The addition of 1-year trastuzumab improved DFS and OS compared with the no trastuzumab group, as shown in other clinical trials. While there were no significant differences in DFS and OS between the trastuzumab-containing arms, cardiac toxicities such as congestive heart failure were significantly less frequent in the non-anthracycline arm (TCH) compared to AC-TH. A long-term follow-up of a median of 10.3 years demonstrated the persistent benefit of additional adjuvant trastuzumab and lower cardiac toxicities in the non-anthracycline arm (TCH) compared to AC-TH.[14] As not only anthracycline, but also trastuzumab could provoke adverse cardiac events, trastuzumab with non-anthracycline-containing chemotherapy would be an effective alternative, especially for patients at greater risk of cardiac toxicities such as those with a pre-existing cardiac problem, obesity, or prior exposure to anthracyclines.

The analysis of NSABP B-31/NCCTG N9831, HERA, and BCIRG-006 trials described above included only node-positive or large tumor patients, which is a high-risk disease, and there were no randomized trials of patients with node-negative or smaller tumors. However, three retrospective analyses demonstrated significantly higher risk of relapse in HER2-positive small, node-negative tumors compared with HER2-negative disease.[15–17] Another retrospective analysis showed significant recurrence-free survival, invasive disease-free survival (IDFS), and OS benefits of adjuvant trastuzumab compared with no trastuzumab in small or node-negative HER2-positive breast cancer patients.[18] In accordance with previous results, a prospective APT trial evaluated adjuvant paclitaxel and trastuzumab in low-risk (tumor size no greater than 3 cm with node-negative disease or one lymph node micrometastasis if an axillary dissection was completed and no further lymph node involvement was identified) HER2-positive breast cancer patients. In the APT trial, adjuvant paclitaxel and trastuzumab showed excellent prognosis, with a 3-year IDFS of 98.7% and 7-year DFS of 93% in low-risk HER2-positive breast cancer patients.[19,20] Despite this outstanding outcome, adjuvant paclitaxel and trastuzumab in low-risk HER2-positive breast cancer patients would be interpreted not as de-escalating therapy, but escalating therapy considering its good prognosis.[21]

In addition to efforts to de-escalate chemotherapy regimens, there have been several trials to reduce

Table 1. Comparison of trials trying to reduce duration of trastuzumab.

Trials	Duration of trastuzumab	Number of patients	Node negative (%)	Hormone receptor positive (%)	Concomitant trastuzumab (%)	Efficacy (*versus* 1-year trastuzumab)	Cardiac events (*versus* 1-year trastuzumab)
SOLD	9 weeks	2174	59.6	66*	100	5-year DFS 88% *versus* 90.5% HR 1.39; 90% CI 1.12–1.72 (non-inferiority margin 1.3)	2% *versus* 3.9%
Short-HER	9 weeks	1253	53.6	68.1	100	5-year DFS 85% *versus* 88% HR 1.13; 90% CI 0.89–1.42 (non-inferiority margin 1.29)	4.3% *versus* 13.1%
PHARE	6 months	3380	54.5	60.9	56.3	2-year DFS 91.1% *versus* 93.8% HR 1.28; 95% CI 1.05–1.56 (non-inferiority margin 1.15)	1.9% *versus* 5.7%
HORG	6 months	481	21	66.7	100	3-year DFS 93.3% *versus* 95.7% HR 1.57; 95% CI 0.86–2.1 (non-inferiority margin 1.53)	0.8% *versus* 0%
PERSEPHONE	6 months	4088	58.3	69.1*	46.6	4-year DFS 89.4% *versus* 89.8% HR 1.07; 90% CI 0.93–1.24 (non-inferiority margin 1.32)	7.8% *versus* 11.4%**

All trials randomized, non-inferiority.
*SOLD, PERSEPHONE ER-positive.
**Clinical cardiac dysfunction.
CI, confidence interval; DFS, disease-free survival; HR: hazard ratio.

the duration of treatment. Although the standard period of adjuvant trastuzumab has been 1 year, there have been several trials shortening this period (Table 1). In the SOLD trial and Short-HER trial, 9-week adjuvant trastuzumab treatment for HER2-positive breast cancer patients failed to prove non-inferiority over that for 12 months. However, cardiac toxicity was less frequent in the 9-week groups.[22,23] In the PHARE and HORG trials, 6-month adjuvant trastuzumab for HER2-positive breast cancer patients failed to demonstrate non-inferiority over 12-month treatment.[24,25] Contrary to these four failed trials, 6-month adjuvant trastuzumab fulfilled non-inferiority over 12 months in 4-year DFS in the PERSEPHONE trial.[26] However, interpretation of the PERSEPHONE results should be cautious because all the other trials with a shortened period of adjuvant trastuzumab failed. If the non-inferiority margin was narrower in the PERSEPHONE trial, as in the other trials, the result of the PERSEPHONE trial would not have been statistically significant.[27] Although the shorter 6-month duration of adjuvant trastuzumab might be appropriate in a specific population, as in the PERSEPHONE trial, this should be decided carefully on a per-patient basis under meticulous consideration including the risk of

recurrence as well as side effects and cost-effectiveness.

Adjuvant dual anti-HER2 treatment with trastuzumab

Other anti-HER2 agents were added to 1-year adjuvant trastuzumab to try to improve the outcomes. Lapatinib is a small molecule that reversibly inhibits tyrosine kinases of HER2 and epidermal growth factor receptor (EGFR). After additional lapatinib on capecitabine had proven to have a significant progression-free survival (PFS) benefit in HER2-positive advanced breast cancer patients compared to capecitabine alone, lapatinib in combination with capecitabine has been a therapeutic option for HER2-positive advanced breast cancer patients who progressed after trastuzumab-containing chemotherapy.[28] In the ALTTO trial, node-positive or high-risk node-negative (tumor size greater than 1 cm) HER2-positive early breast cancer patients were randomized to receive adjuvant treatment with trastuzumab alone, trastuzumab and lapatinib in combination, or trastuzumab followed by lapatinib for 52 weeks. However, lapatinib in addition to trastuzumab did not significantly improve DFS.[29]

Neratinib is a small-molecule, irreversible tyrosine kinase inhibitor of EGFR, HER2, and HER4. It has shown efficacy in HER2-positive advanced breast cancer patients and improved efficacy in early breast cancer patients.[30,31] In the ExteNET trial, 1 year of oral neratinib was administered to early breast cancer patients who had completed neoadjuvant or adjuvant trastuzumab-based therapy. One additional year of extended adjuvant therapy with neratinib significantly increased 2-year IDFS to 93.9% compared with 91.6% in the placebo group.[32] This benefit persisted after a median follow-up of 5.2 years, with a 5-year IDFS of 90.2% in the neratinib arm compared to 87.7% in the placebo group.[33] Especially in HR-positive patients in whom neratinib was given within 1 year of prior trastuzumab, a significant 5-year IDFS benefit was shown. In addition, a similar trend was observed in high-risk patients with residual disease after neoadjuvant treatment.[34] Consequently, adjuvant neratinib following trastuzumab within 1 year is considered for high-risk HR-positive/HER2-positive breast cancer patients. Diarrhea was the most common side effect of neratinib, with 40% of patients experiencing grade 3 diarrhea and 17% discontinuing the drug due to diarrhea. However, preemptive prophylaxis with loperamide, budesonide, and colestipol, alone or in combination, and dose escalation of neratinib reduced the occurrence of neratinib-related diarrhea.[35]

Pertuzumab is another HER2-targeting monoclonal antibody that binds HER2 at a different epitope of the extracellular domain and prevents HER2 from dimerizing with other HER receptors.[36] In the CLEOPATRA trial, pertuzumab plus trastuzumab plus docetaxel significantly prolonged PFS and OS compared to trastuzumab plus docetaxel in HER2-positive metastatic breast cancer patients.[37,38] From this promising effect in the metastatic setting, this dual anti-HER2 targeting was attempted in an adjuvant setting. In the APHINITY trial, node-positive or high-risk node-negative (tumor size greater than 1 cm or greater than 0.5 cm in the presence of a high-risk feature such as histologic or nuclear grade 3 or HR negativity) HER2-positive early breast cancer patients were randomized to receive pertuzumab or placebo and trastuzumab plus chemotherapy (anthracyclines, cyclophosphamide followed by taxanes or docetaxel plus carboplatin). Adjuvant dual anti-HER2 targeting with pertuzumab and trastuzumab significantly improved 3-year IDFS without increasing cardiac toxicities.[39] Subsequent analysis with a 74-month median follow-up confirmed this IDFS benefit, especially in the node-positive group and HR-positive group.[40] A longer follow-up, up to 15 years, is ongoing to fully evaluate the OS benefit. From these results, adjuvant pertuzumab and trastuzumab with chemotherapy is a standard of care in node-positive HER2-positve breast cancer in the latest National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines as of 2021.[41,42]

Adjuvant T-DM1

T-DM1 is an antibody–drug conjugate of HER2-targeting trastuzumab and emtansine, which is a cytotoxic microtubule inhibitor.[43] In addition to the antitumor effect of trastuzumab, release of a cytotoxic microtubule inhibitor has an additional antitumor effect when this agent approaches target cells bearing HER2 with trastuzumab. After its efficacy was proven in metastatic HER2-positive breast cancer, it showed better efficacy than trastuzumab in an adjuvant setting of residual invasive HER2-positive breast cancer.[44–46] In the KATHERINE trial, early breast cancer

patients with residual disease after taxane-based neoadjuvant therapy with trastuzumab were randomly assigned to receive T-DM1 or trastuzumab for 14 cycles.[47] Three-year IDFS was significantly better in the T-DM1 group than in the trastuzumab group (hazard ratio 0.5, $p < 0.001$). In a subgroup analysis from the KATHERINE trial, the benefit of 3-year IDFS with T-DM1 was consistent regardless of tumor HR status or adjuvant radiotherapy, while that of patients receiving trastuzumab with negative HR showed the worst IDFS. However, given the hazard ratio of 0.66 is higher in the subgroup including ypT0, ypT1mic, and ypTis than in subgroups without ypT0, ypT1mic, or ypTis (hazard ratio of 0.29 in ypT4 subgroup, 0.34 in ypT1, ypT1c, 0.4 in ypT3, and 0.5 in ypT2), adjuvant T-DM1 might be skipped in cases with little to no residual cancer burden (RCB). Although 8.3% of HER2-positive patients in pre-neoadjuvant biopsy were HER2 negative on retesting of surgical sample data, a similar better result of T-DM1 *versus* trastuzumab was shown.[48] Subsequent subgroup analysis revealed the benefit of T-DM1 across patient subgroups, including high-risk tumors and small tumors. T-DM1 also did not increase the overall risk of central nervous system recurrence compared to the trastuzumab group. Moreover, T-DM1 showed consistent efficacy regardless of type of neoadjuvant chemotherapy.[49] Based on these results, adjuvant T-DM1 is a standard of care in residual HER2-positive breast cancer patients after neoadjuvant treatment and surgery in the latest NCCN and ESMO guidelines as of 2021.[41,42]

The ATEMPT trial compared adjuvant T-DM1 *versus* adjuvant paclitaxel and trastuzumab in low-risk (tumor size smaller than 2 cm and node negative or one lymph node with micrometastasis) HER2-positive breast cancer patients, which is a current standard in early HER2-positive breast cancer patients based on the results of the APT trial as described above, regarding toxicity profile and efficacy. Although 1 year of adjuvant T-DM1 showed 97.8% 3-year IDFS, clinically relevant toxicity of T-DM1 was similar to that of adjuvant paclitaxel and trastuzumab and failed to demonstrate reduced toxicity of T-DM1.[50]

Dual anti-HER2 treatment with T-DM1 and pertuzumab was also tried. In the KAITLIN trial, node-positive or high-risk node-negative (tumor size larger than 2 cm and HR negative) HER2-positive breast cancer patients were randomly assigned to anthracycline-based chemotherapy followed by 18 cycles of T-DM1 plus pertuzumab or taxane and trastuzumab plus pertuzumab.[51] However, it failed to show a benefit in 3-year IDFS rate.

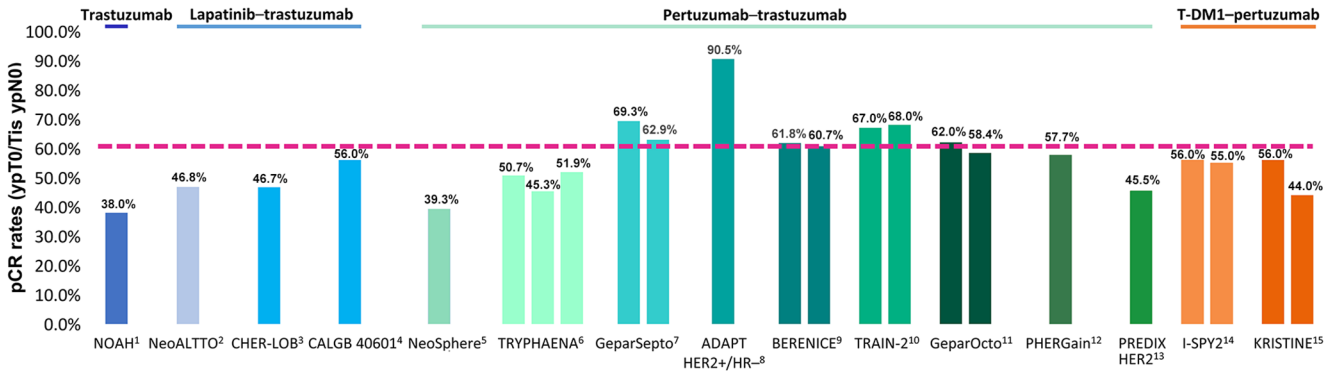
Concurrent adjuvant endocrine therapy

HR-positive/HER2-positive and HR-negative/HER2-positive breast cancers are two different biological subgroups that have distinct natural courses, responses to treatment, and clinical outcomes.[52] Although HR-negative/HER2-positive breast cancer has worse DFS compared with HR-positive/HER2-positive breast cancer with or without anti-HER2 treatment, adjuvant trastuzumab reduces the risk of relapse in HER2-positive breast cancer regardless of HR status.[53] In addition, HR-negative/HER2-postive breast cancer patients are likely to have a slightly higher response to anti-HER2 treatment compared with HR-positive/HER2-positive patients.

In the SOFT and TEXT trials of premenopausal and HR-positive/HER2-positive early breast cancer patients, tamoxifen plus ovarian suppression improved DFS and OS compared with tamoxifen alone.[54] There was no difference in DFS between tamoxifen and aromatase inhibitor groups in the latest meta-analysis including premenopausal and postmenopausal HR-positive/HER2-positive early breast cancer patients.[55] However, not all patients in these analyses received anti-HER2 treatment because it was not the standard of care at that time.

Concurrent adjuvant endocrine therapy with anti-HER2 treatment is the current standard of care for HR-positive/HER2-positive breast cancer patients. Additional research is needed to determine optimal hormone therapy with anti-HER2 treatment.

In conclusion, adjuvant trastuzumab with or without pertuzumab for 1 year in combination with concomitant chemotherapy has become a standard treatment in high-risk node-negative tumors or node-positive HER2-positive early breast cancer patients without residual disease or who have not received neoadjuvant treatment. In particular, adjuvant trastuzumab with pertuzumab is the standard of care for node-positive patients. The risk of cardiac toxicities should be considered when administering trastuzumab, especially with anthracycline-containing chemotherapy. For low-risk HER2-positive early breast



Phase	III[1]	III[2]	II[3]	III[4]	II[5]	II[6]			III[7]		II[8]	II[9]		III[10]		III[11]		II[12]	II[13]	II[14]		III[15]	
*n**	117	152	46	118	107	73	75	77	199	197	42	199	201	219	219	192	190	71	99	31	52	221	223
Regimen	AT/H – T/H – CMF/H	LH – T/LH	T/LH – FEC/LH	T/LH	Doc/PH	FEC/PH – Doc/PH	FEC – Doc/PH	DocCb/PH	nab T/PH – EC/PH	T/PH – EC/PH	T/PH	ddAC – T/PH	FEC – Doc/PH	FEC/PH – TCb/PH	TCb/PH	E – T/PH – C/PH	TLd/PH	DocCb/PH	Doc/PH	T/PH	KP	DocCb/PH	KP
Duration of anti-HER2 therapy (weeks)	33	18	24	16	12	18	9	18	24		12	12		27		12	18	18	18	12		18	

Figure 1. Summary of pCR rates for several trials of HER2-directed therapy.
tpCR in NOAH, ypT0 ypN0 in TRYPHAENA.
C, cyclophosphamide; Cb, carboplatin; D, doxorubicin; dd, dose dense; Doc, docetaxel; E, epirubicin; F, fluorouracil; H, trastuzumab; HER2, human epidermal growth factor receptor 2; K, trastuzumab emtansine (T-DM1); L, lapatinib; Ld, liposomal doxorubicin; M, methotrexate; P, pertuzumab; pCR, pathologic complete response; T, paclitaxel.
1. Gianni L, *et al.* Lancet 2010; 2. José B, *et al.* Lancet 2012; 3. Valentina G, *et al.* J Clin Oncol 2016; 4. Lisa AC, *et al.* J Clin Oncol 2016; 5. Gianni L, *et al.* Lancet Oncol 2012; 6. Schneeweiss A, *et al.* Ann Oncol 2013; 7. Loibl S, *et al.* Ann Oncol 2017; 8. Nitz UA, *et al.* Ann Oncol 2017; 9. Swain SM, *et al.* Ann Oncol 2018; 10. van Ramshorst MS, *et al.* Lancet Oncol 2018; 11. Schneeweiss A, *et al.* Eur J Cancer 2019; 12. José Manuel P, *et al.* Lancet Oncol 2021; 13. Thomas H, *et al.* JAMA Oncol 2021; 14. Amy S. C, *et al.* Nat Commun 2021; 15. Sara AH, *et al.* Lancet Oncol 2018.

cancer patients, adjuvant paclitaxel and 1-year trastuzumab are possible alternatives. For residual disease after neoadjuvant treatment, adjuvant T-DM1 for 14 cycles is a standard treatment. Adjuvant endocrine therapy is added for HR-positive/HER2-positive early breast cancer.

Neoadjuvant HER2 treatment

Neoadjuvant chemotherapy for breast cancer became routine practice due to several advantages. Neoadjuvant chemotherapy provided an opportunity for breast conserving surgery rather than modified radical mastectomy and sentinel lymph node biopsy without extensive lymph node dissection.[56] Specifically, a pathologic complete response (pCR) has become a successful surrogate marker that has a correlation with event-free survival (EFS), DFS, and OS, especially in HER2-positive (non-luminal) and triple-negative tumors.[57–60] These two subtypes were also associated with higher pCR rates to neoadjuvant chemotherapy in a meta-analysis.[61] Consequently, many trials were conducted to achieve higher pCR rates for better outcomes in HER2-positive breast cancer (Figure 1).

Neoadjuvant trastuzumab

In the NOAH trial, neoadjuvant chemotherapy with trastuzumab doubled the pCR rate compared with that of neoadjuvant chemotherapy alone in HER2-positive locally advanced or inflammatory breast cancer (38% *versus* 19%, $p=0.001$).[62] The neoadjuvant chemotherapy regimens consisted of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil. The benefit of pCR-associated EFS was sustained in the additional trastuzumab group in the longer term follow-up analysis.[63]

Neoadjuvant dual anti-HER2 treatment with trastuzumab

Other anti-HER2 agents were added to trastuzumab to achieve higher pCR rates in the neoadjuvant setting.

Lapatinib was tried in neoadjuvant-setting trials. In the NeoALTTO trial, neoadjuvant chemotherapy with lapatinib and trastuzumab showed a higher pCR rate compared with neoadjuvant chemotherapy with either trastuzumab or lapatinib (46.8% *versus* 27.6% *versus* 20%, $p = 0.0007$).[64] However, this benefit did not extend to significantly better clinical outcomes of 6-year EFS and OS in a subsequent analysis.[65] Similar results were found in the CHER-LOB trial. Although a significantly higher pCR rate was achieved in the combined lapatinib and trastuzumab group than in the trastuzumab or lapatinib alone groups, the combined lapatinib and trastuzumab group showed a better trend only in 9-year recurrence-free survival.[66,67] In contrast, the results of neoadjuvant chemotherapy with lapatinib and trastuzumab opposed the results in the CALGB 40601 trial. Although the pCR rate was higher with combined lapatinib and trastuzumab than with trastuzumab alone, the difference was not significant.[68] However, relapse-free survival and OS at 7 years were significantly improved with combined lapatinib and trastuzumab compared with trastuzumab.[69] In conclusion, dual anti-HER2 targeting with lapatinib and trastuzumab in the neoadjuvant setting showed inconsistent results.

Pertuzumab was also added to trastuzumab in several neoadjuvant-setting trials that included patients with HER2-positive, operable, locally advanced, or inflammatory breast cancer with primary tumors larger than 2 cm. In the NeoSphere trial, pertuzumab and trastuzumab plus docetaxel had a significantly improved pCR rate of 39.3% compared with trastuzumab plus docetaxel, pertuzumab plus docetaxel, or pertuzumab plus trastuzumab, which also showed a correlation with 5-year PFS and DFS.[70,71] In the TRYPHAENA trial, patients were randomized to receive 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel (T) with trastuzumab and pertuzumab (HP) concurrent with FEC and docetaxel (Arm A: FECHP → THP) or with docetaxel (Arm B: FEC → THP); or docetaxel, carboplatin with trastuzumab and pertuzumab (Arm C: TCHP). The pCR rates were promising (61.6% (Arm A), 57.3% (Arm B), and 66.2% (Arm C)), and cardiac toxicity was low even in the anthracycline-containing dual anti-HER2 treatment arms (Arm A and Arm B).[72] Long-term DFS and PFS were similar among treatment arms, and pCR was associated with DFS.[73] In the BERENICE trial, patients were randomized to receive either dose-dense doxorubicin and cyclophosphamide followed by paclitaxel or FEC followed by docetaxel and pertuzumab and trastuzumab concurrent with taxanes. The groups demonstrated similar pCR rates (above 60%), and cardiac toxicity was low.[74] In the final analysis, 5-year EFS and OS were similar between the two groups, reaching around 90% and 95%, respectively.[75] Many trials using dual anti-HER2 therapy with pertuzumab and trastuzumab in the neoadjuvant setting have shown pCR rates around 60% or greater, while cardiac toxicity was rare and toxicity was well managed.[76–84] Among them, the TRAIN-2 trial evaluated the neoadjuvant backbone chemotherapy regimens while administering concurrent trastuzumab and pertuzumab in stage II–III HER2-positive breast cancer patients. These regimens consisted of FEC followed by paclitaxel and carboplatin or paclitaxel and carboplatin without anthracycline. While pCR rates between anthracycline and non-anthracycline groups were similar, grade 3 or worse febrile neutropenia was more frequent in the anthracycline group.[78,79] In a subsequent analysis, 3-year EFS and OS were similar, demonstrating that trastuzumab and pertuzumab with anthracycline-omitting chemotherapy can be considered.[80] Neoadjuvant dual blockade with trastuzumab and pertuzumab plus weekly paclitaxel for 12 weeks showed a pCR rate of 90.5% in the WSG-ADAPT HER2+/HR- phase II trial.[81] In the PHERGain trial, dual anti-HER2 agents of trastuzumab and pertuzumab with or without docetaxel and carboplatin were given neoadjuvantly for two cycles to HER2-positive stage I–IIIA, invasive, operable breast cancer patients using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (F-PET/CT) to identify the response. Although trastuzumab and pertuzumab with chemotherapy showed significantly better pCR rates than the trastuzumab and pertuzumab group, pCR rates between F-PET/CT responders and non-responders in the trastuzumab and pertuzumab group were not significantly different (37.9% in F-PET/CT responders *versus* 25.9% in F-PET/CT non-responders, $p = 0.068$), demonstrating a possibility of de-escalating or escalating neoadjuvant treatment depending on F-PET/CT response.[82]

Neoadjuvant T-DM1

Neoadjuvant T-DM1 was administered solely without chemotherapy in the PREDIX HER2 trial.[85] HER2-positive breast cancer patients with tumors larger than 2 cm or lymph node

metastases were randomized to receive T-DM1 alone or docetaxel, trastuzumab, and pertuzumab. Neoadjuvant T-DM1 alone showed comparable pCR with a more favorable toxic profile.

T-DM1 was also tested in dual anti-HER2 therapy regimens. In the I-SPY2 trial, stage II or III HER2-positive breast cancer patients, with tumor size larger than 2.5 cm, were randomized to receive either T-DM1 plus pertuzumab; paclitaxel, trastuzumab, and pertuzumab; or paclitaxel and trastuzumab; all three groups were followed by doxorubicin/cyclophosphamide.[83] Both the T-DM1 plus pertuzumab group and the paclitaxel, trastuzumab, plus pertuzumab group showed significantly better pCR rates than the paclitaxel and trastuzumab group. However, when comparing T-DM1 plus pertuzumab with a regimen of docetaxel, carboplatin, and trastuzumab plus pertuzumab in the KRISTINE trial, neoadjuvant systemic chemotherapy with trastuzumab and pertuzumab resulted in a significantly higher pCR rate than did T-DM1 plus pertuzumab (pCR rate of 55.7% *versus* 44.4%, $p = 0.016$).[84] In subsequent analysis, the 3-year EFS was consistently worse in the group who received T-DM1 plus pertuzumab than in the systemic chemotherapy with trastuzumab and pertuzumab group.[86] Because HER2 heterogeneity might influence the lower pCR rate in the T-DM1 plus pertuzumab group, it should be considered when administering T-DM1 plus pertuzumab without conventional chemotherapy.[87]

Neoadjuvant atezolizumab

Incorporating atezolizumab in neoadjuvant treatment is under investigation. In the Impassion050 trial, neoadjuvant atezolizumab or placebo was administered with dual anti-HER2 treatment and chemotherapy in HER2-positive breast cancer patients who have a very high risk of recurrence.[88] Because atezolizumab showed an unfavorable risk–benefit profile compared with placebo, the trial terminated early.

Biomarkers for predicting pCR

Because pCR is a surrogate marker for EFS, DFS, and OS in HER2-positive breast cancer, there have been many efforts to identify biomarkers to predict pCR (Table 2). However, none have been validated for use in a real-world setting. Further research is needed to develop and validate potential biomarkers.

DFS; disease-free survival; IDFS, invasive DFS; pCR, pathologic complete response; TILs, tumor-infiltrating lymphocytes.

PIK3CA mutation was significantly associated with lower pCR rate among HER2-positive breast cancer patients in a meta-analysis, mainly in HR-positive and dual anti-HER2 treatment population.[89] However, this lower pCR rate did not extend to meaningfully worse DFS. Considering this, although PIK3CA could be a potential biomarker for predicting pCR, further research is needed for validation and to develop novel treatments such as PI3K inhibitors to increase the pCR rate.[90]

Tumor-infiltrating lymphocytes (TILs) have been another potential biomarker predicting pCR in HER2-positive breast cancer patients receiving neoadjuvant treatment. In one meta-analysis, higher baseline TILs were significantly associated with higher pCR rate regardless of anti-HER2 agents and chemotherapy.[91] In other studies, changes in TILs between baseline and post-neoadjuvant treatment were emphasized even though results were incompatible. Although the magnitude of decrease in TIL was strongly related to pCR in one study, the immune-enriched group (an increase in TIL level from $\leqslant 10\%$ to $>10\%$, or a persistent level $>10\%$) achieved significantly higher pCR, EFS, and OS rates compared with the immune-poor group (a decrease in TIL from $>10\%$ to $\leqslant 10\%$, or a persistent level $<10\%$).[92,93] In another study including all subtypes of early breast cancer, increases in TILs and CD 8+ T cells in response to neoadjuvant chemotherapy were associated with pCR, and on-treatment immune response was more predictive of outcome than baseline immune features, although both were strongly correlated.[94] Therefore, further studies are needed before TILs can be used as a precise biomarker for predicting treatment response.

The HER2-enriched subtype was significantly associated with pCR in all patients regardless of HR status in one meta-analysis.[95] Moreover, chemotherapy-free anti-HER2 neoadjuvant therapy provided significantly higher pCR in the HER2-enriched subtype in this analysis. This suggests that HER2-enriched subtype is a biomarker to de-escalate neoadjuvant anti-HER2 treatment. In another study, HER2-enriched subtype and ERBB2 expression were combined and the HER2-enriched and ERBB2-high group showed higher pCR compared with other groups, which suggests that combining HER2-enriched

Table 2. Biomarkers for predicting pCR.

Biomarkers	Outcomes	Limitation and note
PIK3CA mutation	Lower pCR	Lower pCR not extended to meaningfully worse DFS
TILs		Conflicting outcomes
Higher baseline TILs	Higher pCR	
Decrease in TIL	Higher pCR	
Immune-enriched group	Higher pCR, EFS, and OS	
HER2-enriched subtype	Higher pCR	Regardless of HR status and chemotherapy containing
Early response	Higher pCR	Early response defined as decrease more than 30% of Ki-67 or low cellularity (<500 invasive tumor cells) in the 3-week biopsy
RNA expression signatures		Distinct gene signatures associated with pCR *versus* IDFS
ERBB2	Higher pCR	
Estrogen receptor pathway signaling	Higher pCR and IDFS	More prominent in chemotherapy-free arm regarding IDFS
PTEN	Lower pCR	
BRCA	Lower IDFS	
Immune response	Higher IDFS	More prominent in chemotherapy-free arm All significant immune response signatures strongly intercorrelated

subtype and ERBB2 mRNA into a single assay could also produce a potential biomarker for de-escalating neoadjuvant therapy.[96] In contrast, there was no pCR in the low HER2 expression (immunohistochemistry 1+/2+ and fluorescence *in situ* hybridization positive) or basal-like subtypes in patients with dual anti-HER2 treatment alone in one study.[97]

Early response, which was defined as a decrease in more than 30% in Ki-67 or low cellularity (<500 invasive tumor cells) on 3-week biopsy, is another possible biomarker for predicting pCR. In the dual anti-HER2 treatment alone arm in the WSG-ADAPT HER2+/HR- phase II trial described above, the pCR rate for non-responders was only 8.3% compared with 44.7% in responders.

The impact of RNA expression signatures for pCR and survival was also described in the same WSG-ADAPT HER2+/HR- phase II trial.[98] While the ERBB2 and estrogen receptor pathway signaling signatures were related to higher pCR, PTEN signature was associated with worse pCR. In terms of IDFS, while BRCAness signature was unfavorable, several gene signatures related to immune response and estrogen signaling were favorable. Only the estrogen receptor signaling gene signature was related to both pCR and IDFS. Thus, several gene signatures related to immune response might be potential biomarkers for de-escalating therapy.

In summary, non-anthracycline chemotherapy with dual anti-HER2 targeting of trastuzumab and pertuzumab represents one of the preferred neoadjuvant regimens to achieve higher pCR rates and better clinical outcomes. Anthracycline-containing chemotherapy with trastuzumab and pertuzumab would be an alternative.

Future perspectives

To improve outcomes in HER2-postive early breast cancer, incorporating new agents such as T-DXd and immunotherapy in adjuvant and neoadjuvant settings is under investigation. In addition, given the benefit and toxicity from anti-HER2 treatment and chemotherapy, continuous efforts to de-escalate neoadjuvant and adjuvant treatments or to select specific patients for escalated neoadjuvant and adjuvant treatments are ongoing (Table 3).

T-DXd

T-DXd is another antibody–drug conjugate of HER2-targeting trastuzumab and deruxtecan; it is a topoisomerase I inhibitor linked by a cleavable peptide. T-DXd has an antitumor effect attributed not only to trastuzumab and release of deruxtecan into HER2-bearing cancer cells *via* trastuzumab, but also to a bystander killing effect due to its highly membrane-permeable characteristics compared to T-DM1.[99] In the DESTINY-Breast01 trial, T-DXd showed durable antitumor activity in HER2-positive metastatic breast cancer patients who received T-DM1.[100] In the DESTINY-Breast03 trial, T-DXd showed significantly better PFS and overall response rate than did T-DM1 in HER2-positive metastatic breast cancer patients treated with trastuzumab and taxane.[101] Following the promising results of T-DXd in HER2-positive metastatic breast cancer patients, there is an ongoing trial evaluating T-DXd in high-risk HER2-positive breast cancer patients with residual invasive breast cancer following neoadjuvant therapy compared with T-DM1, which is the current standard (NCT04622319, DESTINY-Breast05 trial). In addition to adjuvant T-DXd, a phase III trial of neoadjuvant T-DXd is ongoing in locally advanced or inflammatory HER2-positive breast cancer patients (NCT05113251, DESTINY-Breast11 trial). This trial compares eight cycles *versus* four cycles of neoadjuvant T-DXd, followed by only paclitaxel and trastuzumab plus pertuzumab or four cycles anthracycline and cyclophosphamide before paclitaxel and trastuzumab plus pertuzumab.

Immunotherapy

In this era of immune-oncology, ongoing trials are exploring adding immune checkpoint inhibitors in perioperative HER2-positive breast cancer. Atezolizumab, an anti-programmed cell death-ligand 1 inhibitor, is under investigation with T-DM1. Although adjuvant T-DM1 improved outcomes in residual invasive disease, certain patient groups including inoperable disease and HR-negative and node-positive disease are still at risk of recurrence. To improve this medically unmet need, one study is evaluating adjuvant atezolizumab or placebo and T-DM1 in HER2-positive breast cancer patients with residual disease following neoadjuvant treatment and surgery (NCT04873362, Astefania trial).

Another trial applied neoadjuvant atezolizumab with dual anti-HER2 treatment and chemotherapy in HER2-positive stage II/III breast cancer (NCT03991878, Neo-PATH).[102] After surgery, adjuvant atezolizumab, trastuzumab and pertuzumab is administered in patients achieving pCR; adjuvant atezolizumab and T-DM1 is administered in patients not achieving pCR. Because atezolizumab showed an overall pCR rate of 61.2% with a modest toxicity profile, further research is needed regarding incorporation of atezolizumab. Several trials are currently evaluating incorporation of immunotherapy in HER2-positive early breast cancer patients.

Trials tailored to various situations

There is an ongoing de-escalating trial evaluating neoadjuvant taxane and dual anti-HER2 agents of pertuzumab and trastuzumab and adjuvant dual anti-HER2 agents in stage II–IIIA breast cancer patients who achieve pCR or adjuvant T-DM1 who do not achieve pCR (NCT04266249, CompassHER2-pCR trial). In the CompassHER2 Residual Disease trial as an extension, residual disease patients who did not achieve pCR after neoadjuvant taxane and dual anti-HER2 targeting of pertuzumab and trastuzumab in stage II–IIIA breast cancer are randomized to a group of T-DM1 *versus* a group of T-DM1 and another HER2-targeting oral tyrosine kinase inhibitor, tucatinib. IDFS is the primary endpoint (NCT04457596). In addition, the role of pan-HER2 inhibitors such as tucatinib in neoadjuvant chemotherapy needs to be determined. Another similar de-escalating trial evaluating a combined subcutaneous fixed dose combination (FDC) of pertuzumab and trastuzumab is ongoing. After neoadjuvant dual anti-HER2 treatment and surgery, adjuvant pertuzumab and trastuzumab subcutaneous FDC or adjuvant T-DM1 with or without anthracycline-based chemotherapy is administered depending on RCB score (NCT04675827, Decrescendo trial).

Table 3. Ongoing perioperative anti-HER2 and immune-oncology trials.

Trials	Setting	Phase	Study description
Neoadjuvant anti-HER2 treatment			
NCT05113251	Neoadjuvant	III	Neoadjuvant T-DXd for eight cycles *versus* T-DXd for four cycles followed by paclitaxel, trastuzumab, and pertuzumab *versus* anthracycline and cyclophosphamide for four cycles followed by paclitaxel, trastuzumab, and pertuzumab in locally advanced or inflammatory HER2+ breast cancer patients
Adjuvant anti-HER2 treatment			
NCT04893109	Adjuvant	II	Adjuvant T-DM1 followed by trastuzumab *versus* paclitaxel and trastuzumab followed by trastuzumab in stage I HER2+ breast cancer patients
NCT04266249	Neoadjuvant ~ Adjuvant	II	Neoadjuvant taxane, trastuzumab, and pertuzumab in stage II-IIIA HER2+ breast cancer patients followed by adjuvant trastuzumab and pertuzumab if pCR is achieved or followed by adjuvant T-DM1 if pCR is not achieved
NCT04675827	Neoadjuvant ~ Adjuvant	II	Neoadjuvant taxane combined with SC FDC of pertuzumab and trastuzumab followed by adjuvant SC FDC of pertuzumab and trastuzumab if pCR is achieved or followed by adjuvant T-D1 if RCB score is 1 or followed by adjuvant anthracycline-based chemotherapy and T-DM1 if RCB score is 2 or greater in HER2+/ER-/node-negative early breast cancer patients
Adjuvant anti-HER2 treatment for non-pCR patients			
NCT04622319	Adjuvant	III	Adjuvant T-DXd *versus* T-DM1 in HER2+ breast cancer patients with residual disease following neoadjuvant therapy
NCT04457596	Adjuvant	III	Adjuvant T-DM1 and placebo *versus* T-DM1 and tucatinib in residual disease patients who did not achieve pCR in stage II-IIIA HER2+ breast cancer
Immune checkpoint inhibitors			
NCT04873362	Adjuvant	III	Adjuvant atezolizumab or placebo and T-DM1 in HER2+ breast cancer patients at high risk of recurrence following preoperative therapy
NCT03991878	Neoadjuvant ~Adjuvant	IB-II	Neoadjuvant atezolizumab, docetaxel, trastuzumab, and pertuzumab followed by adjuvant atezolizumab, trastuzumab, and pertuzumab *versus* atezolizumab and T-DM1 depending on pCR status in HER2+ breast cancer patients
Omitting surgery			
NCT04578106	Omitting surgery	II	Omitting surgery in low-risk HER2+ early breast cancer patients if there is a complete response after standard anti-HER2-based neoadjuvant therapy with paclitaxel, trastuzumab, and pertuzumab

HER2+, human epidermal growth factor receptor 2 positive; pCR, pathologic complete response; RCB, residual cancer burden; SC FDC, subcutaneous fixed dose combination; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

The ongoing randomized phase II ATEMPT 2.0 trial, which compares adjuvant T-DM1 followed by trastuzumab *versus* paclitaxel and trastuzumab followed by trastuzumab in stage I HER2-positive invasive breast cancer patients seeks to determine whether T-DM1 followed by trastuzumab will have fewer side effects and better clinical benefits (NCT04893109).

Moreover, there is an ongoing phase II trial to omit surgery in low-risk HER2-positive early breast cancer patients. In HER2-enriched/ERBB2-high breast cancer patients according to PAM50 intrinsic subtype, loco-regional surgery is omitted if there is a complete response after dual anti-HER2 neoadjuvant therapy of paclitaxel, trastuzumab, and pertuzumab (NCT04578106, ELPIS trial).

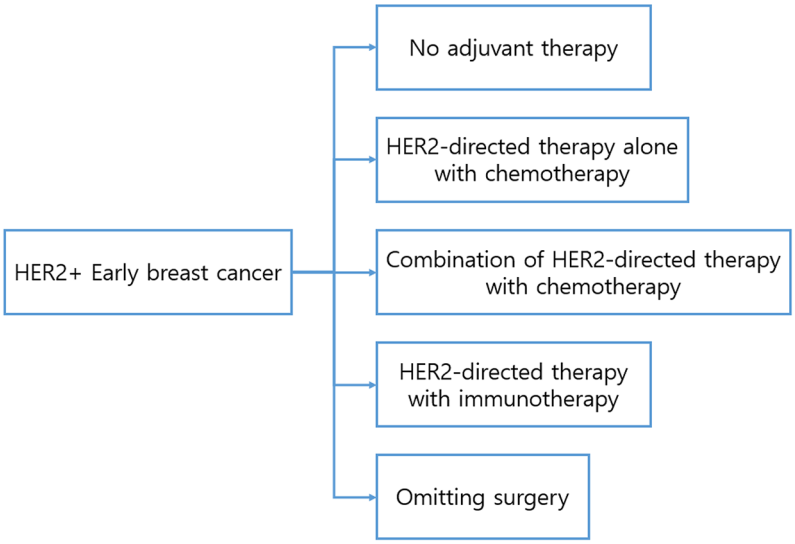


Figure 2. Tailored treatment for HER2+ early breast cancer.
HER2+, human epidermal growth factor receptor 2 positive.

Discussion

As of 2021, pCR rates are approximately 60% or more, and long-term outcomes are correlated with pCR rates in HER2-positive breast cancer patients. Thus, neoadjuvant treatment with HER2 targeting is preferred in HER2-postive early breast cancer patients if the tumor is larger than 2 cm. To improve outcomes, several clinical trials are ongoing, and there is much attention on the Destiny-Breast11 trial incorporating T-DXd in the neoadjuvant setting based on the promising results of its use in metastatic settings.

After groundbreaking development of trastuzumab for HER2-positive breast cancer patients, subsequent novel drugs such as pertuzumab, neratinib, T-DM1, and T-DXd have been developed and used in various settings alone or in combination. In addition, immune checkpoint inhibitors are under investigation to improve the outcomes. To achieve higher pCR rates in early HER2-positive breast cancer patients and lower recurrence and progression rates in patients with residual disease, relevant data are accumulating. The current anti-HER2 treatment strategy is likely to change depending on the results of ongoing and planned clinical trials. In the future, tailored treatments such as no adjuvant therapy, various HER2-directed therapies alone with chemotherapy, combinations of various HER2-directed therapies and chemotherapy, addition of immune checkpoint inhibitors, and omission of surgery will be individualized in HER2-positive early breast cancer patients (Figure 2).

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Author contributions

Joohyun Hong: Conceptualization; Writing – original draft; Writing – review & editing; Visualization.

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