Updates on targeting human epidermal growth factor receptor 2-positive breast cancer: what's to know in 2021

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Purpose of review
To highlight recent practice changing clinical trials, focusing on those leading to new drug approvals, in human epidermal growth factor receptor 2-positive (HER2+) breast cancer.

Recent findings
The improved disease-free survival of adjuvant trastuzumab emtansine (T-DM1) over trastuzumab in patients with residual disease has made neoadjuvant sequencing of therapy standard for most patients with early stage disease. In patients with metastatic HER2+ breast cancer, trastuzumab deruxtecan has recently shown dramatically improved efficacy over T-DM1. Tucatinib is an oral tyrosine kinase inhibitor with best in class blood-brain barrier penetration. Margetuximab, a novel HER2-targeted chimeric monoclonal antibody with an engineered Fc receptor designed to activate local immune response, was recently approved in heavily pretreated patients based on modest but significant improvement in progression-free survival.

Summary
Patients with HER2+ breast cancer have a variety of therapeutic options in the early stage and metastatic setting. Optimal sequencing of therapy will depend on patient-specific factors such as site of tumor progression and underlying comorbidities. De-escalation of the first-line metastatic regimen may be considered in select patients with hormone positive/HER2+ breast cancer, by using endocrine therapy instead of chemotherapy in combination with HER2-targeted therapy, which may improve side effects without sacrificing efficacy.

Keywords
antibody-drug conjugate, breast cancer, human epidermal growth factor receptor 2, targeted therapy

INTRODUCTION

Since human epidermal growth factor receptor 2 amplified (HER2+) breast cancer was first described by Slamon *et al.* [1], multiple targeted therapies have been developed that have dramatically improved survival in this high-risk population. Over the past couple years in particular, new drug approvals have greatly expanded upon the efficacy HER2-targeted therapy. Given the number of options available, particularly in metastatic disease, the optimal choice and sequence of therapy will often depend on factors unique to each patient. This review will focus on important contemporary topics in both early and advanced stage HER2+ breast cancer from a medical oncology perspective and will summarize the most important trials recently published or reported as of late 2021.

UPDATES IN EARLY STAGE DISEASE MANAGEMENT

Though some controversy persists, pathologic complete response (pCR) is generally considered a valid surrogate endpoint for improved disease-free survival (DFS) in HER2+ and triple negative breast cancer [2–6]. As important as pCR is as an endpoint, lack of pCR (or residual disease after neoadjuvant chemotherapy) identifies a high-risk population that may derive additional benefit from a change

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KEY POINTS

- Neoadjuvant chemotherapy should be considered for most patients with early stage HER2+ breast cancer.
- T-Dxd has drastically improved efficacy over T-DM1, though toxicity (especially pulmonary toxicity) remains an important concern.
- Tucatinib is a HER2-specific oral TKI with excellent blood brain barrier penetration.
- Margetuximab is a novel therapy that engages the immune system and was recently approved based on progression-free survival.

in therapy postsurgery. The KATHERINE trial was a randomized, open-label trial in patients ($N = 1486$) with residual invasive HER2+ clinical stages I–III breast cancer after neoadjuvant taxane and trastuzumab-based chemotherapy [7]. Patients received either adjuvant trastuzumab (standard of care) or trastuzumab emtansine (T-DM1, intervention). Those with clinical stage T1aN0 and T1bN0 were excluded. Patients who were randomized to T-DM1 experienced an absolute improvement in 3-year DFS of 11.3% over those who were randomized to trastuzumab (88.3% vs 77.0%, respectively), corresponding to a 50% improvement in survival (hazard ratio, HR, 0.50, 95% confidence interval, CI, 0.39–0.64, $P < 0.001$). Although more adverse events leading to discontinuation occurred in the T-DM1 group (18.0%) than the trastuzumab group (2.1%), most patients who discontinued T-DM1 switched to trastuzumab and completed a total of 14 cycles of therapy.

The results of KATHERINE were immediately practice changing and led to the Federal Drug Administration (FDA) approval of T-DM1 in the adjuvant setting [8]. The degree of potential benefit offered by this 'response adapted' approach should prompt all oncologists to consider a neoadjuvant regimen for patients represented in the KATHERINE trial design (i.e. HER2+ tumors > 1 cm or node positive) [9], though the national comprehensive cancer network (NCCN) guidelines recommend reserving neoadjuvant therapy for patients with tumors >2 cm [10]. Because the adjuvant ExteNET trial, which showed a small benefit of adjuvant neratinib in patients with hormone receptor positive (HR+)/HER2+ high-risk breast cancer [11], was performed in the pre-KATHERINE era, the additional benefit of neratinib in patients who receive adjuvant T-DM1 is currently unknown. It is reasonable to discuss adjuvant neratinib in patients with high-risk HR+/HER2+ disease.

Though adjuvant T-DM1 has become standard in the adjuvant setting in cases of residual disease after neoadjuvant chemotherapy, other studies have explored the use of T-DM1 in the neoadjuvant setting and in the low-risk adjuvant setting. KRISTINE was a phase 3 trial of neoadjuvant T-DM1 plus pertuzumab vs docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) in patients with stages II–III HER2+ breast cancer, with a primary endpoint of pCR rate [12]. KRISTINE showed that while T-DM1 plus pertuzumab was associated with less toxicity, TCHP maintained a superior rate of pCR (55.7% vs 44.4%, $P = 0.016$). TCHP was associated with a higher rate of pCR regardless of hormone receptor status, therefore remains the standard of care for neoadjuvant regimens. In the ATEMPT trial, patients with stage I HER2+ breast cancer who had undergone curative intent surgery were randomized to receive either adjuvant T-DM1 every 3 weeks for 17 cycles or paclitaxel plus trastuzumab (TH) weekly for 12 weeks followed by trastuzumab every 3 weeks for 39 weeks [13]. Although T-DM1 was associated with excellent 3-year DFS (97.8%) which was very similar to prior reports for adjuvant TH in the adjuvant paclitaxel trastuzumab trial (3-year DFS 98.7%), the percentage of patients experiencing a clinically relevant toxicity (the co-primary endpoint) was similar between T-DM1 and TH (46% vs 47%). Given this lack of benefit over TH with regard to toxicity or efficacy, adjuvant TH remains the most commonly used regimen when de-escalation of therapy in low risk HER2+ early breast cancer is being considered.

ANTIBODY-DRUG CONJUGATES IN METASTATIC DISEASE

With the introduction of trastuzumab as the first HER2-targeted therapy in HER2+ breast cancer [14], drug development began to shift away from cytotoxic chemotherapy and began to focus on interrupting the aberrant cell signaling pathway relevant in this subtype of cancer. However, with the development of T-DM1, the first approved antibody-drug conjugate in HER2+ breast cancer [15], multiple therapies are being developed that utilize the killing effect to powerful cytotoxic agents in a targeted manner, using HER2 to gain entry into the cell [16].

T-DM1 has, until recently, retained its position in the second-line metastatic setting based on the results of the EMILIA study based on significantly improved PFS, OS, and toxicity as compared to lapatinib [15]. A second antibody-drug conjugate, trastuzumab deruxtecan (T-Dxd), differs from T-DM1 in its linker, cytotoxic payload, drug to antibody ratio, and the ability to produce a 'bystander

effect' in which nearby, HER2-cells also seem to be impacted by the drug [17]. T-Dxd at a dose of 5.4 mg/kg every 3 weeks was approved by the FDA based on the objective response rate (ORR, 60.9%) seen in the single arm, open label, phase 2 DESTINY-Breast01 study in patients with pretreated metastatic HER2+ breast cancer in the third-line setting [18].

Although the ORR in DESTINY-Breast01 was impressive, it remained a single-arm phase 2 trial, and randomized evidence was still pending. Recently, the results of the randomized DESTINY-Breast03 study were reported at the European Society of Medical Oncology (ESMO) 2021 annual meeting (Abstract LBA1). DESTINY-Breast03 randomized patients with metastatic HER2+ breast cancer who had progressed on a first-line taxane and trastuzumab containing regimen to receive either T-Dxd or T-DM1. At 16 months of follow-up, progression-free survival (PFS) by blinded independent central review was drastically improved in the T-Dxd arm as compared to the T-DM1 arm (not yet reached vs 6.8 months, HR 0.28, 95% CI 0.22–0.37, $P = 7.8 \times 10^{-22}$). This benefit was maintained across subgroups, and preliminary OS analysis also suggests significant improvement with T-Dxd. ORR was also significantly improved with T-Dxd over T-DM1 (79.7% vs 34.2%, $P < 0.0001$).

Although T-Dxd has proven to be extremely efficacious, it is not without toxicity. In DESTINY-Breast03, increased toxicity was seen as compared to T-DM1 with regard to any drug-related treatment emergent adverse events (TEAE, 98.1% vs 86.6%), grade ≥3 TEAE (45.1% vs 39.8%), TEAE leading to drug discontinuation (12.8% vs 5.0%). One of the most important adverse effects with T-Dxd that has emerged since the phase 1 studies has been interstitial lung disease (ILD)/pneumonitis (SPECIFIC CITATION). In DESTINY-Breast01, 13.6% of patients experienced any grade ILD/pneumonitis, including 4 patients who died due to drug-related ILD/Pneumonitis. In a combined analysis of multiple trials recently presented at ESMO (abstract 920), the overall rate of ILD/pneumonitis (adjudicated by central committee) was 15.5%, with a total of 12.2% being grade 1–2, and 2.4% resulting in death. Interestingly, there is a lower rate of grade 3/4 toxicity as compared to grades 1–2 or 5 toxicity, suggesting that early detection and intervention is crucial in this population. In DESTINY-Breast03, whereas 9.7% of patients in the T-Dxd arm experienced grade 1/2 ILD/pneumonitis, and only 0.8% experienced grade 3, and no patients were reported to have grade 4 or 5 events. Since ILD/pneumonitis has become a recognized AE of interest, independent adjudication committees have been implemented in the trials to keep close watch over any suspected cases, underscoring the importance of close monitoring and a low threshold for evaluating for any lung disease early in this high-risk population.

TUCATINIB AND CENTRAL NERVOUS SYSTEM METASTASES

One of the biggest challenges in treating HER2+ breast cancer remains the development of central nervous system (CNS) metastases, which develop in up to half of patients [19–23]. Tucatinib, a HER2-specific tyrosine kinase inhibitor (TKI), showed promising activity in a phase 1b study in patients with and without CNS metastases [24]. HER2CLIMB was a phase 2, double-blind, placebo-controlled, randomized trial in patients with metastatic HER2+ breast cancer progressed on two lines of therapy, including T-DM1 [25]. Patients were randomized to receive capecitabine plus trastuzumab and either tucatinib (300 mg twice daily) or placebo. Importantly, this study did not compare tucatinib to another TKI containing regimen. The addition of tucatinib over placebo to capecitabine and trastuzumab resulted in improved PFS (7.8 vs 5.6 months, $P < 0.001$), improved rate of PFS at 1 year (33.1% vs 12.3%, $P < 0.001$), and improved rate of OS at 2 years (44.9% vs 26.6%, $P = 0.005$). For patients with CNS metastases, tucatinib was also associated with improved CNS-PFS (9.9 vs 4.2 months, HR 0.32, 95% CI 0.22–0.48, $P < 0.001$), improved intracranial ORR (47.3% vs 20.0%, $P = 0.03$) [26]. Toxicity with tucatinib, capecitabine, and trastuzumab is comparable to the previously reported toxicity profile of capecitabine and TKIs, which includes diarrhea, palmar-plantar erythema, nausea/vomiting, and fatigue [25]. Tucatinib was approved by the FDA after 1 prior line of therapy in the metastatic setting, which allows for patients to access this drug if their primary site of progression is in the CNS.

ENGAGING THE IMMUNE SYSTEM IN HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 POSITIVE DISEASE

Although trastuzumab works via disruption of cell signaling pathways, other compounds have sought to combine this mechanism with the engagement of the immune system. Margetuximab is a chimeric monoclonal antibody targeting HER2 in a fashion similar to trastuzumab, but with an engineered Fc domain designed to increase local activation of innate and adaptive immunity [27,28]. This Fc domain exerts activity on immune effector cells by having increased affinity of the activating Fcγ receptor CD16A (FcγRIIIa), as well as decreased affinity for the inhibitory Fcγ receptor CD32B

(FcγRIIb). Additionally, margetuximab binds especially well to the CD16A-158F allele, which is found in about 85% of the population [29,30].

To test the relative efficacy of margetuximab as compared to trastuzumab in the relapsed/refractory metastatic setting, SOPHIA randomized 536 patients who had progressed on two or more prior anti-HER2 agents to receive cytotoxic chemotherapy of physician's choice plus either margetuximab (15 mg/kg) or trastruzumab (standard dosing) [31]. The primary endpoints were PFS and OS. Margetuximab plus chemotherapy marginally, but statistically significantly, improved PFS over trastuzumab plus chemotherapy (5.8 vs 4.9 months, HR 0.76, 95% CI 0.59–0.98, $P = 0.03$). There was also significantly improved ORR with the margetuximab arm over the trastuzumab arm (25% vs 14%, $P < 0.01$). Interim OS analysis did not show a difference between the two groups, but final OS analysis is still pending. Safety endpoints were similar between the two arms. Exploratory endpoints by CD16A genotype preliminarily suggest a small additional benefit in CD16A-F carriers. Based on the results of SOPHIA, the FDA approved margetuximab in December 2020 for patients with HER2+ metastatic breast cancer who had received at least two prior lines of HER2-based therapy.

DE-ESCALATION IN METASTATIC 'TRIPLE POSITIVE' DISEASE

Given the effectiveness of HER2-targeted therapies, de-escalation of the partner chemotherapy has been a theme in many clinical trials [12,32,33]. The results of the phase 3, noninferiority sysucc-002 trial were reported at ASCO 2021 [34]. Patients ($n = 392$) with previously untreated metastatic hormone receptor positive, HER2+ breast cancer were randomized to receive either chemotherapy plus trastuzumab or endocrine therapy + trastuzumab, with the primary endpoint being PFS with a noninferiority margin of a HR of 1.35. Median PFS in the endocrine therapy arm was noninferior (and numerically improved) as compared to the chemotherapy arm (19.2 months vs 14.8 months, HR 0.88, $p_{\text{non-inferiority}} = < 0.0001$). As expected, toxicity was much worse in the chemotherapy arm. This supports the NCCN recommendation for either chemotherapy or endocrine therapy, plus HER2-targeted therapy, as the first-line recommendation. Although many oncologists will begin with taxane plus HER2-targeted therapy and peel off the taxane after a few cycles, the specific regimen should be individualized to the patient with toxicity and benefit in mind, and endocrine therapy plus HER2-targeted therapy should be considered in patients who may be especially at risk of significant adverse events.

CONCLUSION

The recent approval of several highly efficacious targeted agents has led to an array of options for patients facing metastatic HER2+ breast cancer. T-Dxd has shown unprecedented activity compared to the current standard second-line (T-DM1), though close monitoring for pulmonary toxicity is crucial. Tucatinib, a HER2-specific TKI, has shown promising intracranial effectiveness in patients with the highest unmet clinical need: brain metastases. Although the absolutely improvement in survival was small, margetuximab is a new option for patients with heavily pretreated disease and may help engage the immune system in novel ways. De-escalation of the partner systemic therapy in first-line setting may be considered in select patients without potentially compromising efficacy. Finally, neoadjuvant therapy has become the standard for most patients with early-stage disease, as it allows for risk stratification and personalized refinement of adjuvant agents. Given the array of approved agents in the metastatic setting, sequencing of therapy has become an important consideration, and patient-specific factors will influence the next best choice of therapy.

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