Abstract: The management of human epidermal growth factor receptor (HER2)-positive breast cancer (BC) has rapidly evolved over the last 20 years. Major advances have led to US Food and Drug Administration approval of 7 HER2-targeted therapies for the treatment of early-stage and/or advanced-stage disease. Although oncologic outcomes continue to improve, most patients with advanced HER2-positive BC ultimately die of their disease because of primary or acquired resistance to therapy, and patients with HER2-positive early BC who have residual invasive disease after preoperative systemic therapy are at a higher risk of distant recurrence and death. The concept of treatment de-escalation and escalation is increasingly important to optimally tailor therapy for patients with HER2-positive BC and is a major focus of the current review. Research efforts in this regard are discussed as well as updates regarding the evolving standard of care in the (neo)adjuvant and metastatic settings, including the use of novel combination therapies. The authors also briefly discuss ongoing challenges in the management of HER2-positive BC (eg, intrinsic vs acquired drug resistance, the identification of predictive biomarkers, the integration of imaging techniques to guide clinical practice), and the treatment of HER2-positive brain metastases. Research aimed at superseding these challenges will be imperative to ensure continued progress in the management of HER2-positive BC going forward.

Keywords: breast cancer brain metastases, de-escalation, human epidermal growth factor receptor 2 (HER2)-positive breast cancer, mechanisms of resistance, (neo)adjuvant therapy

Introduction

In 2020, approximately 276,480 invasive breast cancers (BCs) will be diagnosed among women in the United States, and approximately 15% to 20% will be human epidermal growth factor receptor 2 (HER2) positive.1,2 Before the advent of the HER2-targeted monoclonal antibody trastuzumab, HER2-positive BC was associated with an aggressive phenotype, with high recurrence rates and inferior survival outcomes.2 By late 2006, results from landmark trials had demonstrated that chemotherapy and trastuzumab significantly improved progression-free survival (PFS) and overall survival (OS) in early and advanced-stage, HER2-positive BC1-6; therefore, trastuzumab-based regimens became the standard of care. Despite these advances, approximately 16% to 22% of patients with early-stage BC (EBC) relapse,7,8 and 22% to 25% of patients with HER2-positive metastatic BC (MBC) display primary (eg, de novo) or secondary (eg, acquired) resistance to HER2-directed therapies.9,10 Therefore, research has focused on strategies to overcome resistance to HER2-directed therapies, with the goal of further improving patient outcomes. Currently, there are 7 US Food and Drug Administration (FDA)—approved, HER2-targeted agents for use in HER2-positive BC in the (neo)adjuvant and/or metastatic settings: trastuzumab; the humanized HER2-targeted monoclonal antibody pertuzumab11,12; the HER1
and HER2 tyrosine kinase inhibitor (TKI) lapatinib; the pan-Her TKI neratinib; the selective HER2-targeted TKI tucatinib; and 2 antibody-drug conjugates (ADCs), trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (DS-8201a) (Table 1) (Fig. 1).

The standard-of-care management of early and advanced, HER2-positive BC is described in detail elsewhere and typically involves HER2-targeted therapy or therapies, often combined with chemotherapy or endocrine therapy. In the landmark CLEOPATRA trial (ClinicalTrials.gov identifier NCT00567190), patients with HER2-positive MBC were randomized to receive first-line treatment with docetaxel, trastuzumab, and pertuzumab or placebo. End-of-study results after 99.9 months of follow-up noted that the median OS was 57.1 months (95% CI, 50–72 months) in the pertuzumab arm and 40.8 months (95% CI, 36–48 months) in the placebo arm (hazard ratio, 0.69; 95% CI, 0.58–0.82); the 8-year landmark OS rates were 37% (95% CI, 31%–42%) in the pertuzumab group and 23% (95% CI, 19%–28%) in the placebo group. Therefore, in the first-line metastatic setting, treatment is usually a taxane in combination with trastuzumab and pertuzumab, and second-line treatment is with T-DM1 based on results from the EMILIA trial (ClinicalTrials.gov identifier NCT00829166). In the third-line setting and beyond, treatment options are less well defined, especially given the recent FDA approvals for neratinib, tucatinib, and trastuzumab deruxtecan. Overall, major progress has been made in the management of patients with HER2-positive BC over the past 20 years, and the median survival for patients with advanced HER2-positive BC now approaches 5 years. However, the standard of care is rapidly evolving, and numerous challenges remain. Despite extensive research incorporating translational science and novel imaging modalities, HER2 remains the only validated predictive biomarker to assist with tailoring therapy. This is a major issue, as the concept of treatment escalation and de-escalation is increasingly important in the management of HER2-positive EBC; the overarching idea is to individualize therapy, maximize efficacy, and reduce unnecessary toxicity. Furthermore, HER2-positive MBC remains incurable, and novel treatment options are needed; results from recently reported trials are changing the treatment paradigm. Finally, up to 50% of patients with advanced, HER2-positive BC develop brain metastases, a devastating diagnosis associated with significant morbidity and mortality as well as limited systemic treatment options. In this article, we review the evolving standard of care in early and advanced, HER2-positive BC, with a focus on de-escalation versus escalation of therapy and on recent FDA-approved agents, which are changing the treatment paradigm.

Therapeutic Advances and Challenges in the Treatment of Early-Stage HER2-Positive BC

Adjuvant/Neoadjuvant Treatment

Seminal trials evaluating the efficacy of chemotherapy plus trastuzumab compared with chemotherapy alone showed unprecedented improvements in PFS and OS (an approximately 50% reduction in recurrence and an approximately 30% improvement in survival) in both adjuvant and metastatic settings, firmly establishing trastuzumab-based regimens as a standard of care in patients with early and advanced, HER2-positive BC (Table 1). Since those trials were reported, polychemotherapy with trastuzumab has remained standard adjuvant treatment for HER2-positive BC. Furthermore, trials evaluating dual HER2-targeted therapy and chemotherapy were associated with superior oncologic outcomes in the adjuvant setting compared with chemotherapy and HER2-targeted therapy alone. Therefore, many adjuvant regimens for HER2-positive BC involve 2 or 3 cytotoxic chemotherapy agents and 1 to 3 HER2-targeted agents, and they take 1 or 2 years to complete. De-escalation was the next logical step in optimizing treatment to decrease toxicities without compromising outcomes, and studies evaluating shorter durations of HER2-directed therapy and de-escalated chemotherapy ensued. The concept of treatment de-escalation is becoming increasingly important as we attempt to balance the benefits versus the risks of systemic therapy. Furthermore, the concept of treatment escalation is also imperative to identify patients with high-risk disease and tailor therapy options accordingly. Specifically, patients with residual, invasive, HER2-positive BC after neoadjuvant chemotherapy and HER2-directed therapy had inferior oncologic outcomes in the NeoALTTO (ClinicalTrials.gov identifier NCT00553358) and Cancer and Leukemia Group B (CALGB) 40601 (ClinicalTrials.gov identifier NCT00770809) trials, with recurrence rates of 35% and 20% at 6 years and 5 years, respectively. Because most patients with residual disease do not relapse, the accurate identification of high-risk patients is important to personalize treatment decisions. In the phase 3 KATHERINE trial (ClinicalTrials.gov identifier NCT01772472; n = 1486), patients with residual, invasive, HER2-positive EBC were randomized 1:1 to receive 14 cycles of postneoadjuvant T-DM1 or trastuzumab. At the 3-year follow-up, patients who received T-DM1 had a 50% reduction in invasive disease or death compared with those who received trastuzumab alone (hazard ratio, 0.5; 95% CI, 0.39–0.64; P < .001). These striking results led to the FDA approval of adjuvant T-DM1 in this setting.

De-escalation in the Adjuvant Setting

The Adjuvant Paclitaxel and Trastuzumab (APT) trial was a phase 2, single-arm study of 410 patients with resected,
| AGENT | MECHANISM OF ACTION | TREATMENT SETTING(S) | LANDMARK TRIALS LEADING TO APPROVAL/NCT NO. | TRIAL REGIMENS | CLINICAL OUTCOMES | YEAR APPROVED |
|-------|---------------------|---------------------|---------------------------------------------|----------------|------------------|---------------|
| Trastuzumab | Humanized MoAb targeted to extracellular juxtamembrane domain of HER2 | Adjuvant HER2+ EBC, first line | NSABP-31/NCT00004067 and N9831/NCT00005970 | AC-T-placebo vs AC-T-H and AC-T vs AC-H vs AC-T-H | Joint analysis: DFS, 75% vs 87% [HR, 0.48; 95% CI, 0.39-0.59; P < .001]; 33% reduction in risk of death [HR, 0.67; 95% CI, 0.48-0.93; P = .015] with sequential trastuzumab (Romond 20053) | 2006 |
| | | | | BCI RG 006/NCT00021255 | ACT vs ACT-H vs TC-H | 5-y DFS, 75% vs 84% [HR, 0.64; P < .001] vs 81% [HR, 0.75; P = .04] (Slamon 201126) | |
| | | | | HERA/NCT00045032 | Observation vs trastuzumab (1 or 2 y) | 10-y DFS: 63% vs 69% [1 y] vs 69% [2 y] (Cameron 20177) | |
| Pertuzumab | Humanized MoAb targeted to HER2 sub-domain II, preventing homodimerization or heterodimerization | Neoadjuvant HER2+, EBC | NeoSphere/NCT00545688 | TD vs PTD vs PT vs PD | pCR (ypT0/is ypN0): PTD vs TD, 39.3% vs 21.5% [P = .0063] (Gianni 201219) | 2013 |
| | | | | Adjuvant HER2+, EBC | APHINITY/NCT01358877 | Chemotherapy plus trastuzumab plus pertuzumab vs placebo | 3-y iDFS, 93.2% vs 94.1% [HR, 0.77; 95% CI, 0.62-0.96; P = .02] (Minckwitz 201720); 6-y iDFS, 87.8% vs 90.6% [HR, 0.72; 95% CI, 0.59-0.87], most notable in lymph node-positive patients (Ricart 202013) | 2017 (Adjuvant) |
| Neratinib | Oral, irreversible TKI of HER1, HER2, and HER4 | Extended adjuvant treatment of HER2+ EBC | ExteNET/NCT00878709 | Placebo vs neratinib | 2-y iDFS; HR, 0.67 [95% CI, 0.50-0.91; P = .0091] favoring neratinib (Chan 201615) | 2017 |
| Ado-trastuzumab emtansine (T-DM1) | ADC with trastuzumab joined to maytansinoid, a potent microtubule-disrupting agent | Adjuvant HER2+ EBC with residual disease after neoadjuvant taxane and trastuzumab-based treatment | KATHERINE/NCT01772472 | Trastuzumab vs T-DM1 | iDFS: HR, 0.50 favoring T-DM1 [95% CI, 0.39-0.64; P < .0001] (Von Minckwitz 201921) | 2019 |

Abbreviations: AC-H, adriamycin (doxorubicin), cyclophosphamide, and trastuzumab; AC-T, doxorubicin, cyclophosphamide, and paclitaxel; AC-T-H, doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab; ADC, antibody-drug conjugate; DFS, disease-free survival; EBC, early breast cancer; H, trastuzumab; HER2, human epidermal growth factor receptor; HR, hazard ratio; iDFS, invasive disease-free survival; MoAb, monoclonal antibody; NCT NO., ClinicalTrials.gov identification number; NSABP, National Surgical and Adjuvant Breast Bowel Project; pCR, pathologic complete response; PD, pertuzumab and docetaxel; PT, trastuzumab and pertuzumab; PTD, pertuzumab, trastuzumab, and docetaxel; TC, docetaxel and cyclophosphamide; TC-H, docetaxel, cyclophosphamide, and trastuzumab; TD, trastuzumab and docetaxel; THP, docetaxel, trastuzumab, and pertuzumab; TKI, tyrosine kinase inhibitor; ypN, pathologic lymph node classification when the patient receives neoadjuvant therapy before undergoing surgical intervention; ypT, pathologic tumor classification when the patient receives neoadjuvant therapy before undergoing surgical intervention.
lymph node–negative, HER2-positive EBC measuring ≤3 cm. A prospective randomized trial was not performed given feasibility issues and because patients and oncologists may have been concerned about the inclusion of a treatment arm omitting trastuzumab. Patients received treatment with paclitaxel and trastuzumab (TH) for 12 weeks, followed by the completion of 1 year of trastuzumab monotherapy. It should be noted that approximately 50% of patients had tumors measuring ≤1 cm, only 9% had tumors measuring 2 to 3 cm, and approximately 65% had hormone receptor (HR)–positive disease. The disease-free survival (DFS) rate at 7 years was 93.3%, and the 7-year recurrence-free interval was 97.5%. Therefore, the APT trial demonstrated that treatment de-escalation is possible in patients with low-anatomic-risk, HER2-positive disease, and further studies evaluating treatment de-escalation ensued.

The phase 2 ATEMPT trial (ClinicalTrials.gov identifier NCT01853748) randomized approximately 500 patients with stage I, HER2-positive BC 3:1 to receive T-DM1 or weekly TH for 12 weeks, followed by the completion of 1 year of trastuzumab monotherapy (ie, the APT regimen). The co-primary endpoints were 3-year DFS in the T-DM1 arm and a toxicity comparison between the treatment arms; it is important to note that the study was not powered for efficacy. In the T-DM1 arm, the 3-year DFS was 97.7% (n = 383), compared with 92.8% in the TH arm (n = 114). The incidence of clinically relevant toxicities was comparable; there was a higher treatment discontinuation rate in the T-DM1 arm but a
higher incidence of neuropathy in the TH arm. Overall, it was concluded that T-DM1 therapy did not reflect de-escalated treatment, and longer term follow-up was needed. The financial toxicity of 1 year of adjuvant T-DM1 compared with the APT regimen was also a concern. However, for selected patients with resected, HER2-positive EBC (eg, patients with preexisting neuropathy/concerns regarding alopecia), 1 year of adjuvant T-DM1 may be an acceptable treatment alternative. Pertinent data regarding quality of life and patient-reported outcomes were reported separately. Overall, ATEMPT was not truly a de-escalation trial, and it is discussed here to highlight the differences between that study and the APT trial.

RESPECT (ClinicalTrials.gov identifier NCT01-104935) was a phase 3, noninferiority, randomized controlled trial comparing trastuzumab monotherapy versus trastuzumab and chemotherapy in elderly patients (aged 70–80 years) with resected stage I through stage IIIA disease. Although this study was underpowered, at 3 years, there was no significant difference in DFS between groups (eg, 94.8% in the trastuzumab plus chemotherapy arm [n = 131] vs 89.2% in the trastuzumab monotherapy arm [n = 135]; P = .35). Of note, most patients (approximately 85%) had stage I or stage II A BC (41.7%). Furthermore, better health-related quality-of-life measures were reported in the trastuzumab monotherapy arm. A key point was that elderly patients do well on chemotherapy and trastuzumab. However, as the difference between the groups was small, trastuzumab monotherapy is a reasonable consideration for those patients who either cannot tolerate or may decline chemotherapy. In summary, continued attempts to de-escalate treatment and evaluate chemotherapy-sparing regimens are appropriate in patients with the most favorable prognosis or in those who are unable to tolerate significant therapy-associated toxicity.

Optimal Duration of Herceptin
The duration of trastuzumab therapy was arbitrarily defined as 1 year in the landmark adjuvant trastuzumab trials, and it remains the accepted standard based on previously established safety and efficacy data. However, several studies have challenged the treatment paradigm. The Finland Herceptin trial (International Standard Randomised Controlled Trial number ISRCTN76560285) randomized 232 patients who had HER2-positive EBC to receive either 9 weeks of trastuzumab plus docetaxel or vinorelbine alone versus 9 weeks of trastuzumab with docetaxel or vinorelbine. Patients who received trastuzumab had a superior DFS at 3 years (89% vs 78%; hazard ratio, 0.42), with a proportional benefit similar to that seen in previous studies in which adjuvant trastuzumab was administered for 1 year. Ultimately, a statistically significant difference in DFS was observed at a 5-year follow-up in patients who received 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) with docetaxel plus trastuzumab versus FEC plus docetaxel alone (DFS: hazard ratio, 0.32; P = .029). Conversely, in the HERA trial (ClinicalTrials.gov identifier NCT0045032), greater than 5000 patients with HER2-positive EBC who had completed adjuvant chemotherapy were randomized to observation or to either 1 year or 2 years of adjuvant trastuzumab. At a median follow-up of 11 years, it was noted that 2 years of trastuzumab conferred no additional benefit compared with 1 year of treatment, and a higher incidence of cardiotoxicity with a longer therapy duration was observed. The Persephone (ClinicalTrials.gov identifier NCT00712140), Short-HER (ClinicalTrials.gov identifier NCT00629278), PHARE (ClinicalTrials.gov identifier NCT00381901), SOLD (ClinicalTrials.gov identifier NCT00593697), and Hellenic Oncology Research Group trials have since investigated a shorter duration of adjuvant trastuzumab, and all but the Persephone trial failed to confirm noninferiority compared with 1 year. However, differences in the results from these trials may be because of noninferiority cutoff values and different definitions of prespecified events. Although 1 year of treatment will likely continue to be the standard recommendation, oncologists may elect to treat some patients (eg, those with underlying cardiac dysfunction) with an abbreviated course of trastuzumab. Given the ongoing coronavirus disease 2019 (COVID-19) pandemic, this approach may also be warranted for selected immunocompromised patients.

Neoadjuvant Treatment De-Escalation
The benefits of neoadjuvant chemotherapy for EBC have been well described by others. The achievement of a pathologic complete response (pCR) to treatment is a surrogate marker of improved oncologic outcomes, especially in HER2-positive BC. Clinical trials evaluating neoadjuvant chemotherapy with or without trastuzumab were conducted, and the addition of trastuzumab more than doubled pCR rates and resulted in superior recurrence-free and event-free survival outcomes, as observed in the adjuvant trials. These results led the way for the routine use of preoperative trastuzumab combined with chemotherapy, particularly for locally advanced tumors. Subsequent trials evaluated dual HER2-targeted therapy using trastuzumab combined with either lapatinib or pertuzumab; note was made of superior pCR rates with dual HER2-targeted therapy compared with trastuzumab alone. Results from the NeoSphere (ClinicalTrials.gov identifier NCT00545688), TRYPHAENA (ClinicalTrials.gov identifier NCT00976989), Berenice (ClinicalTrials.gov identifier NCT02132949), and West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy (ADAPT) (ClinicalTrials.gov identifier NCT01817452) trials set the precedent for the routine use of dual HER2-targeted therapy with pertuzumab.
and trastuzumab in conjunction with neoadjuvant chemotherapy. In 2013, accelerated approval was granted for the use of neoadjuvant pertuzumab, representing a landmark decision by the FDA. 58

Because many patients with HER2-positive EBC have an excellent outlook with modern treatments, attempts to safely de-escalate treatment are ongoing. 59 The neoadjuvant platform is a useful way to de-escalate (or escalate) therapy based on whether or not a pCR is achieved.60 The CompassHER2-pCR trial (EA1181; ClinicalTrials.gov identifier NCT04266249) will test the ability to de-escalate therapy among patients who have an excellent response to neoadjuvant, HER2-targeted therapy. Eligible patients with HER2-positive EBC will receive 12 weeks of preoperative therapy with a taxane, trastuzumab, and pertuzumab; no additional chemotherapy will be given to patients who achieve a pCR. CompassHER2-pCR will test the hypothesis that a pCR after de-escalated therapy will result in a 3-year recurrence-free survival rate ≥92%. The results from this trial will likely have a meaningful impact on clinical practice and future research.

An important step toward expediting drug development and tailoring therapy in the neoadjuvant setting is I-SPY2 (ClinicalTrials.gov identifier NCT01042379), a multicenter, adaptively randomized trial in which multiple experimental drugs are simultaneously tested against standard treatment; patients are assigned to therapy based on the molecular signature of their tumors. 61 Agents progress to phase 3 evaluation when they reach a predetermined threshold of efficacy, whereas drugs unlikely to improve pCR rates are dropped from the trial. HER2-targeted agents tested in I-SPY include tucatinib, neratinib, T-DM1 and pertuzumab, MK-2206, and AMG 386 (further clinical development of the latter 2 agents is not being pursued in HER2-positive BC). The study design allows researchers to evaluate therapies quickly and in smaller groups of patients. No novel HER2-targeted agents are being evaluated at the current time.

Chemotherapy-Free Regimens

Given that approximately 17% and approximately 30% of participants, respectively, treated with pertuzumab and trastuzumab alone in the NeoSphere and ADAPT trials achieved a pCR, 54, 56 there has been considerable interest in further evaluating neoadjuvant chemotherapy-free regimens in HER2-positive EBC. In the phase 3 KRISTINE trial (ClinicalTrials.gov identifier NCT02131064), participants with stage II and stage III, HER2-positive EBC were randomized to receive either T-DM1 plus pertuzumab or docetaxel, carboplatin, and trastuzumab plus pertuzumab (TCHP). 62 The pCR rate was significantly higher in the TCHP arm compared with the T-DM1-P arm (55.7% vs 44.4%), but numerically more grade 3 and 4 adverse events (AEs) and serious AEs (SAEs) occurred in the TCHP arm. It was subsequently reported that outcomes were excellent in all study participants who achieved a pCR, 63 which suggests that de-escalation to a chemotherapy-free regimen is possible for selected patients. Clearly, there is a subset of patients who may do very well with chemotherapy-free regimens, but the identification of accurate biomarkers of response is critical. In the phase 2 Translational Breast Cancer Research Consortium (TBCRC) 026 study (ClinicalTrials.gov identifier NCT01937117), measurements of tumor maximum standardized uptake values corrected for lean body mass on [18F]fluorodeoxyglucose–positron emission tomography (FDG-PET)/computed tomography (CT) were predictive of a pCR in patients with HR-negative, HER2-positive EBC who received 4 cycles of neoadjuvant pertuzumab and trastuzumab. 64 Once optimized, this strategy may assist with tailoring treatment in this setting.

NA-PHER2 (ClinicalTrials.gov identifier NCT02-530424) was a phase 2 study of neoadjuvant palbociclib, trastuzumab, pertuzumab, and fulvestrant in patients with HR-positive, HER2-positive BC. 65 The coprimary endpoints were the change from baseline in Ki67 expression at 2 weeks on treatment and at surgery and the changes in apoptosis from baseline to surgery. The secondary endpoints were the clinical objective response and pCR rates. Significant reductions in Ki−67 levels were noted after 2 weeks on treatment and at surgery (in both Ki−67 levels and apoptosis). Of 30 evaluable patients, 8 (27%) had a pCR in breast and axillary lymph nodes. 65 PALTAN (ClinicalTrials.gov identifier NCT02907918) is a phase 2 neoadjuvant trial of palbociclib, letrozole, and trastuzumab in stage II and stage III, estrogen receptor (ER)-positive, HER2-positive BC; the results are expected in 2021.

Escalating Therapy in the Curative Intent Setting—Adjuvant Treatment

Although many patients have excellent oncologic outcomes after receipt of (neo)adjuvant HER2-directed therapy and chemotherapy, others remain at considerable risk of local and/or distant BC recurrence. 38 Therefore, subsequent clinical trials focused on strategies to further improve DFS and OS outcomes for higher risk patients (eg, patients with larger tumors or with lymph node–positive and/or postoperative residual invasive disease after preoperative systemic therapy). Adjuvant trials evaluating an extended course of trastuzumab (HERA), lapatinib (ALL TO), or bevacizumab (BETH; ClinicalTrials.gov identifier NCT00625898) in combination with standard chemotherapy and trastuzumab did not result in a statistically significant increase in OS compared with chemotherapy and trastuzumab alone. 7, 66, 67 The ExteNET trial (ClinicalTrials.gov identifier NCT00878709) noted a 2.5% DFS advantage in patients with stage II and stage III, HER2-positive EBC who received 1 year of adjuvant neratinib after the completion of chemotherapy and adjuvant trastuzumab; the DFS benefit
was greater in those with HR-positive, HER2-positive EBC (4.4%). These results led to FDA approval of adjuvant neratinib in 2017. However, there are limited data to support the use of neratinib in patients who received pertuzumab and T-DM1 postoperatively. Furthermore, the incidence of severe diarrhea in ExteNET participants was considerable (grade 3 in 40%), although the development of prophylactic antidiarrheal regimens has mitigated this toxicity. Results of the landmark KATHERINE trial, which led to the FDA approval of adjuvant T-DM1, are described above.

In 2017, the FDA approved the use of adjuvant pertuzumab in combination with chemotherapy and trastuzumab for high-risk, HER2-positive EBC (eg, HR-negative and/or lymph node–positive tumors). This approval was based on the primary analysis of the APHINITY trial (ClinicalTrials.gov identifier NCT01358877), in which approximately 4800 patients with resected, HER2-positive EBC were randomized 1:1 to receive chemotherapy and pertuzumab plus either placebo or pertuzumab. Despite the significant benefits observed in the neoadjuvant and metastatic settings when pertuzumab was added to chemotherapy and trastuzumab, at a 4-year follow-up, only a modest 1.7% invasive DFS (iDFS) advantage was noted in the pertuzumab arm, with a distant recurrence benefit of 1.1%. The benefit was greater in patients with lymph node–positive and HR-negative disease, with ∆Δ2.2% and ∆Δ2.3%, respectively. Updated results from APHINITY noted that, at 6 years, the iDFS advantage increased to 2.8% in the pertuzumab arm; patients with lymph node–positive disease had a 4.5% iDFS benefit. Interestingly, it was also noted that patients with HR-positive and HR-negative disease benefitted from adjuvant pertuzumab with longer follow-up (DFS, 3.0%). The incidence of grade 3 diarrhea was higher in the pertuzumab arm (9.8% vs 3.7%), and no new cardiac safety issues were noted. Central nervous system (CNS) recurrences accounted for a substantial proportion of recurrences (range, 25%-33%) and, unfortunately, the incidence was similar in both treatment arms. Therefore, lymph node–positive patients, irrespective of HR status, are candidates for adjuvant pertuzumab in addition to chemotherapy and trastuzumab. However, in 2020, most patients with HER2-positive EBC receive neoadjuvant therapy. Standard neoadjuvant regimens incorporate pertuzumab and, although they are based on APHINITY, the benefit in patients with clinically lymph node–negative disease is unclear. A potential advantage is an increased pCR rate, which reduces the requirement for adjuvant T-DM1.

Postneoadjuvant Trials (Escalation)

Although treatment with adjuvant T-DM1 has resulted overall in improved iDFS outcomes for patients with residual, invasive, HER2-positive breast cancer, patients with ER-negative and/or lymph node–positive disease have inferior iDFS outcomes and may benefit from trials evaluating further therapy escalation. The phase 3 CompassHER2 RD trial (A011801: ClinicalTrials.gov identifier NCT04457596) aims to further improve iDFS in this subset by randomizing participants 1:1 to receive 14 cycles of T-DM1 and tucatinib and/or placebo. The incidence of breast cancer brain metastases (BCBM) in both treatment arms will be noted; this trial will activate in late 2020. Another trial (ClinicalTrials.gov identifier NCT04197687) is a phase 2 study that aims to evaluate immune-related biomarkers for pCR in HER2-positive EBC. Participants with residual disease after neoadjuvant therapy are randomized 2:1 to receive either T-DM1 and a multiepitope vaccine or T-DM1 and placebo. The primary study endpoints are iDFS and safety.

Therapeutic Advances and Challenges in the Treatment of Advanced HER2-Positive BC

Metastatic HER2-Positive BC

Currently, standard first-line treatment for patients with HER2-positive MBC is a taxane, trastuzumab, and pertuzumab. The final CLEOPATRA results after 8 years of follow-up show a sustained response to first-line treatment with taxane, trastuzumab, and pertuzumab, with a median OS of 37% for the combined taxane, trastuzumab, and pertuzumab group compared with 23% in the combined taxane, trastuzumab, and placebo group, with a similar long-term toxicity profile. Given these results, the question of when to discontinue HER2-directed therapy in the setting of a sustained radiologic complete response to therapy is a pertinent question; further research is needed to identify patients in whom trastuzumab may safely be discontinued. T-DM1 was FDA approved on the basis of the EMILIA trial and is typically administered in the second-line metastatic setting. In the third-line setting and beyond, treatment options are less well defined and include trastuzumab plus chemotherapy, lapatinib plus capecitabine, lapatinib plus trastuzumab, trastuzumab plus capecitabine, and endocrine therapy plus HER2-directed therapy. The standard of care is rapidly evolving, with the recent FDA approvals of trastuzumab deruxtecan (DS-8201a), neratinib, and tucatinib; margosertib is currently under review by the FDA (Table 2). Other regimens under evaluation include combinations with immunotherapy, CDK4/CDK6 inhibitors, novel antibody-drug conjugates, other TKIs, and novel HER2-targeted antibodies. Relevant data regarding the aforementioned agents (approved and investigational) are outlined in below (Table 3) (Fig. 1).
| AGENT                        | MECHANISM OF ACTION | LINE OF THERAPY | LANDMARK TRIALS/S/NCT NO. | TRIAL REGIMENS                                      | CLINICAL OUTCOMES                                                                 | YEAR APPROVED |
|------------------------------|---------------------|-----------------|--------------------------|-----------------------------------------------------|-----------------------------------------------------------------------------------|---------------|
| Trastuzumab                  | See Table 1         | ≥ Second line   | Slamon 2011<sup>3</sup>  | Chemotherapy vs chemotherapy plus trastuzumab       | Median TTP, 4.6 mo vs 7.4 mo [P < .001]; OS, 45% vs 29% [P < .001] (Slamon 2011<sup>3</sup>) | 1998          |
| Pertuzumab                  | See Table 1         | First line      | Cobleigh 1999<sup>2</sup> | Trastuzumab                                         | ORR, 15% (Cobleigh 1999<sup>2</sup>)                                                  | 2012          |
| Lapatinib                    | Oral reversible TKI | ≥ Second line   | GlaxoSmithKline/ NCT00078572 | Capecitabine vs L plus capecitabine                 | Median TTP, 4.4 mo vs 8.4 mo [HR, 0.49; 95% CI, 0.34-0.71; P < .001] (Geyer 2006<sup>13</sup>) | 2007          |
| Ado-trastuzumab emtansine    | See Table 1         | ≥ Third line    | EGF104900/NCT00320385    | L vs L plus H                                       | PFS, 2.1 mo vs 3.0 mo [HR, 0.71; 95% CI, 0.52-0.98; P = .027]; CBR, 12.4% vs 24.7% [P = .01] (Blackwell 2010<sup>13</sup>) | 2013          |
| Trastuzumab deruxtecan       | ADC with trastuzumab joined to topoisomerase I inhibitor | ≥ Third line | DESTINY-Breast01/ NCT03248492 | T-DM1                                               | ORR, 60.9% [95% CI, 53.4%-68.0%]; median PFS, 16.4 mo [95% CI, 12.7-NR] (Modi 2019<sup>18</sup>) | 2019          |
| Neratinib                    | Oral, irreversible TKI of HER1, HER2, and HER4 | ≥ Third line | NALA/NCT0180573 (Saura 2019<sup>14</sup>) | Neatinib plus capecitabine [N+C]; lapatinib plus capecitabine [L+C] | 6-mo PFS, 47.4% vs 37.8% [N+C vs L+C]; 6-mo OS, 90.2% vs 87.5%                                           | 2020          |
| Tucatinib                    | Highly selective HER2 TKI | ≥ Third line | Her2CLimb/NCT02614794 (Murthy 2020<sup>15</sup>) | Tastuzumab plus capecitabine plus placebo vs trastuzumab plus capecitabine plus tucatinib | Median PFS, 5.6 mo vs 7.8 mo [HR, 0.54; 95% CI, 0.42-0.71]; median OS, 17.4 mo vs 21.9 mo [HR, 0.66; 95% CI, 0.50-0.88] | 2020          |

Abbreviations: ADC, antibody-drug conjugate; CBR, clinical benefit rate; H, trastuzumab; HER2, human epidermal growth factor receptor; HR, hazard ratio; L, lapatinib; MBC, metastatic breast cancer; NCT NO., ClinicalTrials.gov identification number; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TH, docetaxel and trastuzumab; THP, docetaxel, trastuzumab, and pertuzumab; TKI, tyrosine kinase inhibitor; TTP, time to treatment progression; ΔOS, difference in overall survival; ΔPFS, difference in progression-free survival.

<sup>a</sup>To come.
### Table 3. Results From Trials Evaluating Novel Therapeutics for HER2-Positive Metastatic Breast Cancer

| CLASS OF DRUG          | MECHANISM OF ACTION                                                                 | TRIAL NAME/NCT NO.          | PHASE | NO. OF PATIENTS | POPULATION                                | REGIMEN                                                                 | OUTCOMES DATA                                                                 | TOXICITY DATA                                               |
|------------------------|--------------------------------------------------------------------------------------|----------------------------|-------|----------------|--------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|
| ADC: Margetuximab      | Anti-HER2 with FCγ-domain, inducing ADCC                                             | SOPHIA/NCT02492711 (Rugo 2019) | 3     | 536            | ≥2 Prior anti-HER2 therapies               | Tastuzumab plus chemotherapy vs margetuximab plus chemotherapy             | PFS, 5.8 mo vs 4.9 mo [HR, 0.76; P = .03]a                         | Grade 3 AEs, 53.7% vs 52.6%a                                  |
| Checkpoint inhibitor:  | Anti-PD-L1 (Emens 2019)                                                              | KATE2/NCT02924883          | 2     | 202            | Prior paclitaxel plus trastuzumab          | TDM-1 vs TDM-1 plus atezolizumab                                         | PFS, 4.1 mo vs 8.5 mo [HR, 0.60; 95% CI, 0.32-1.11] in PD-L1+ subgroup; 1-y OS, 89.0% vs 89.1% in PD-L1+ subgroup | Grade 3 AEs, 41% vs 44%; thrombocytopenia, 4% vs 13%; atezolizumab: pyrexia, 5%; abdominal pain, 3%; seizures, 3% |
| Checkpoint inhibitor:  | Avelumab                                                                             | JAVELIN/ NCT01772004 (Dirix 2018) | 1b    | 168            | ≥3 Prior anti-HER2 therapies, including T-DM1 | Avelumab                                                                 | Overall ORR, 3.0%; 53% in TNBC³                                 | Grade ≥3 AEs, 13.7%; 2 treatment-related deaths              |
| Pembrolizumab          | Anti-PD-L1                                                                            | PANACEA/NCT02129556 (Loi 2019) | 2     | 58             | Tastuzumab-resistant disease               | Tastuzumab with or without pembrolizumab                                   | NP                                                           | Grade 3-5 AEs, including dyspnea, pneumonitis, and pericardial effusion³ |
| ADC: SYD985            | Combines specificity of trastuzumab and duocarmazine, a DNA alkylating agent        | TULIP/NCT03262935 (Saura 2018) | 3     | 345 (Recruitment complete)                   | ≥2 Prior lines of therapy, including T-DM1                                | Physician’s choice vs SYD985                                           | ORR, 33%; median PFS, 9.4 mo, from phase 1 data              | fatigue and neutropenia, 6%; conjunctivitis, 4%               |
| ADC: ZW25              | Binds to the ECD4 of HER2 (trastuzumab) and ECD2 (pertuzumab) (Meric-Bernstam 2017) | ZW25/ NCT028921230         | 1     | 234            | Advanced HER2+ cancer that has progressed after HER2-directed therapies | ZW25 + chemotherapy                                                       | NP                                                           | Infusion reactions, 5 of 9; diarrhea, 4 of 9; fatigue, 3 of 9 |
| Oral TKI: Pozotinib    | Nonspecific inhibitor of HER1, HER2, and HER4                                       | NOV120101-203/ NCT02418689 (Kim 2018) | 2     | 106            | Prior taxane and 2 HER2-directed therapies | Pozotinib                                                                | Median PFS, 4.04 mo; PIK3CA-mutated had shortened duration of survival [HR, 2.25; 95% CI, 1.39-3.63; P = .001] | Diarrhea, 96.23%; stomatitis, 92.45%; rash, 63.21% (Park 2018³) |
| Oral TKI: Pyrotinib    | Inhibitor of HER1 and HER2 (Pernas & Tolaney 2019)                                  | PHOEBE/ NCT03080805         | 3     | 240            | Prior treatment with trastuzumab, ≤2 chemotherapy regimens in the metastatic setting | Laptatinib plus capecitabine vs pyrotinib plus capecitabine                | NP                                                           | Diarrhea, 30.8% vs 12.8%; hand-foot syndrome, 15.7% vs 5.3%   |
|                        | Jiangsu HengRui Medicine/ NCT02973737 (Jiang 2019)                                 |                             | 3     | 350            | Prior treatment with trastuzumab, anthocyanine and taxane | Arm 1, pyrotinib plus capecitabine; arm 2, placebo capecitabine            | Median PFS, 11.1 mo vs 4.1 mo [95% CI, 9.66-6.53 mo] | Diarrhea, 30.8% vs 12.8%; hand-foot syndrome, 15.7% vs 5.3%   |
| CLASS OF DRUG      | MECHANISM OF ACTION | TRIAL NAME/NCT NO.                          | PHASE | NO. OF PATIENTS | POPULATION                                                                                     | REGIMEN                                                                 | OUTCOMES DATA                                                                                      | TOXICITY DATA                                                                                          |
|-------------------|---------------------|--------------------------------------------|-------|----------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| CDK4i/CDK6i:      | Palbociclib         | PATRICIA/NCT02448420 (Ciruelos 2019<sup>6</sup>) | 2     | 232            | ≤4 Lines, including trastuzumab, lapatinib, neratinib, pertuzumab, or T-DM1 with chemotherapy | Tastuzumab plus palbociclib with or without letrozole; cohort A, ER-negative; cohort B1, ER-positive; cohort B2, ER-positive with letrozole | 6-mo PFS: cohort A, 33.3%; cohort B1, 40.6%; cohort B2, 53.3%                                           | Grade 1-2 AEs, 97.7%; grade 3-4 AEs, 84.4%; neutropenia, 80%; thrombocytopenia, 17%                        |
| CDK4i/CDK6i:      | Ribociclib          | DFCI/NCT02657343 (Spring 2019<sup>7</sup>)  | 1b/2  | 26             | HR+/HER2+ MBC: cohort A, prior trastuzumab and taxane, but not T-DM1; cohort B, prior trastuzumab, pertuzumab, T-DM1; cohort C, prior trastuzumab, pertuzumab, and T-DM1 with a maximum of 5 prior lines for MBC | Ribociclib plus T-DM1 plus trastuzumab plus fulvestrant               | Median PFS, 12.5 mo [95% CI, 10.5-20.9 mo]                                                            | Neutropenia, 50%; infection, 20%; anemia, 10%; thrombocytopenia, 10%                                |
| CDK4i/CDK6i:      | Abemaciclib         | monarcher/NCT02675231 (Tolaney 2020<sup>8</sup>) | 2     | 237            | ≥2 Prior anti-HER2 therapies, including T-DM1 and taxane                                      | Arm A, abemaciclib plus fulvestrant; arm B, abemaciclib plus trastuzumab; arm C, trastuzumab plus physician’s choice chemotherapy | Median PFS in cohort A vs C, 8.3 mo vs 5.7 mo [HR, 0.673; 95% CI, 0.451-1.003; P = .0253]           | Neutropenia, 26.9%, 22.1%, and 26.4%; leukopenia, 10.3%, 2.6%, and 9.7%; thrombocytopenia, 10.3%, 6.5%, and 2.8%; diarrhea, 9.6%, 6.5%, and 2.8%, respectively |
| PI3K inhibitor:   | Alpelisib           | MSKCC/NCT02167854 (Shah 2015<sup>9</sup>)   | 1     | 23             | Prior pertuzumab and T-DM1                                                                  | Alpelisib plus LIM716 plus+ trastuzumab                                 | ORR, 33%; median PFS, 9.4 mo<sup>1</sup>                                                            | Diarrhea, hyperglycemia, hypokalemia, mucositis, transaminitis                                        |
| Selectively inhibits PIK3Ca | Northwestern University/NCT02038010 (Jain 2018<sup>10</sup>) | 1     | 17             | Progression on prior trastuzumab plus taxane                                              | T-DM1 plus alpelisib                                                    | Median PFS, 6 mo                                                                                      | Hyperglycemia, rash, weight loss, pancreatitis                                                          |

Abbreviations: DFCI, Dana-Farber Cancer Institute; ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; AEs, adverse events; ECD, extracellular domain; ER, estrogen receptor; HER2, human epidermal growth factor receptor; HR, hazard ratio; LR, limited recruitment; MBC, metastatic breast cancer; MSKCC, Memorial Sloan Kettering Cancer Center; NCT NO., ClinicalTrials.gov identification number; NP, data not published; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, recruiting; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer.

<sup>1</sup>Preliminary data were published in meeting abstracts.
Trastuzumab deruxtecan (DS-8201a)

Trastuzumab deruxtecan is a humanized, HER2-targeted IgG1 monoclonal antibody linked with a topoisomerase I inhibitor payload and a tetrapeptide-based, cleavable linker; preclinical and clinical activity was noted in T-DM1-resistant and HER2-low tumors.\(^{89,90}\) Results from the phase 2 Destiny-Breast01 trial (ClinicalTrials.gov identifier NCT03248492) evaluating trastuzumab deruxtecan (DS-8201a) in 168 patients with heavily pretreated, HER2-positive MBC were recently reported.\(^{18}\) All participants had received prior trastuzumab and T-DM1, 66% had received prior pertuzumab, and 54% had received other HER2-targeted therapies. The overall response rate (ORR) was 60.9% (95% CI, 53.4%-68.0%), with a disease control rate of 97.3% (95% CI, 93.8%-99.1%), and the median PFS was 16.4 months (95% CI, 12.7 months to not evaluated).\(^{18}\) Common AEs included low-grade cytopenias and gastrointestinal toxicities; a notable SAE was the development of interstitial lung disease (eg, 25 cases [13.6%] in 184 patients treated at the FDA-approved dose of 5.4 mg/kg, including 4 fatalities). Therefore, careful education of providers and patients is imperative to ensure awareness and appropriate management of this potential SAE. Trastuzumab deruxtecan was FDA approved in December 2019 for patients with HER2-positive MBC who have received ≥2 HER2-targeted regimens in the metastatic setting; results from the DESTINY-Breast02 (trastuzumab deruxtecan vs treatment of physician’s choice [third-line]; ClinicalTrials.gov identifier NCT03523585), DESTINY-Breast03 (trastuzumab deruxtecan vs T-DM1 [second-line]; ClinicalTrials.gov identifier NCT03529110), and DESTINY-Breast04 (HER2-low MBC; ClinicalTrials.gov identifier NCT03734029) trials will also be informative.

Tucatinib

The oral, potent, HER2-specific TKI tucatinib selectively inhibits HER2 and demonstrates activity as monotherapy or combined with chemotherapy or trastuzumab in HER2-positive murine xenograft models, including intracranial tumor xenograft models.\(^{91}\) Results from a phase 1 study of tucatinib in HER2-positive advanced solid tumors, with an expansion cohort of patients who had HER2-positive MBC (n = 43), noted a lower incidence and severity of diarrhea and rash with tucatinib than that usually associated with dual HER2/EGFR inhibitors, as well as significant antitumor activity in patients with heavily pretreated, HER2-positive MBC.\(^{92}\) Subsequently, the HER2CLIMB study (ClinicalTrials.gov identifier NCT02614794) randomized 612 patients 2:1 to receive capecitabine, trastuzumab, and either tucatinib or placebo. All participants had received prior T-DM1, pertuzumab, and trastuzumab. Almost 50% had BCBM, and approximately 40% had untreated or previously treated and progressing BCBM, which was a unique aspect of this trial. Patients randomized to the tucatinib arm had a median PFS of 7.8 months versus 5.6 months in the control arm (hazard ratio, 0.54; \(P < .00001\)) and a median OS of 21.9 months versus 17.4 months (hazard ratio, 0.66; \(P < .00480\)). The median PFS in patients with BCBM was also superior in the tucatinib arm (7.6 months vs 5.4 months; hazard ratio, 0.48; \(P < .00001\)). Importantly, the median PFS at 1 year was 24.9% in the tucatinib arm and 0% in the placebo arm (hazard ratio, 0.48; 95% CI, 0.34-0.69; \(P < .001\)). The toxicity profile was as expected, with slightly higher rates of grade ≥3 diarrhea, aspartate and alanine aminotransferase levels, and palmar-plantar erythrodyssesthesis in the tucatinib arm. Tucatinib received FDA approval in April 2020, and CNS-specific endpoints will be reported later. A trial of tucatinib, trastuzumab, and capecitabine in HER2-positive leptomeningeal disease is currently recruiting participants (ClinicalTrials.gov identifier NCT03501979).

Neratinib

Neratinib is a potent, low-molecular-weight, orally administered pan-HER TKI; preclinical studies have shown increased potency compared with lapatinib.\(^{93}\) Neratinib is approved in the adjuvant setting based on results of the ExteNet trial.\(^{14,94}\) In the phase 3 NALA trial (ClinicalTrials.gov identifier NCT01808573), 621 patients with HER2-positive MBC who had received ≥2 prior lines of HER2-directed therapy for metastatic disease were randomized 1:1 to receive either neratinib and capecitabine or lapatinib and capecitabine.\(^{74}\) Given concern for cumulative gastrointestinal toxicity, the capecitabine dose was lower in the neratinib arm, and patients took anti-diarrheal prophylaxis. Approximately one-third of patients had received prior T-DM1, trastuzumab, and pertuzumab. Centrally confirmed PFS favored the neratinib arm (8.8 months vs 6.6 months; \(P = .00003\)), and OS outcomes were also numerically superior (24.0 months vs 22.2 months; \(P = .0066\)). There was also a delayed time to intervention for and reduced cumulative incidence of brain metastases in the neratinib arm (overall cumulative incidence, 22.8% vs 29.2%; \(P = .043\)). Neratinib and capecitabine were FDA approved for patients with HER2-positive MBC who have received ≥2 prior HER2-based regimens in the metastatic setting in February 2020.\(^{68}\)

Margetuximab

Margetuximab is an HER2-targeted antibody with an engineered FC\(\gamma\) domain and was designed to induce antibody-dependent cellular toxicity.\(^{75,95}\) In vitro data showed that margetuximab increased the ability to induce antibody-dependent cellular toxicity regardless of FC\(\gamma\)R isoform through optimized binding to HER2-expressing tumor cells.\(^{95}\) The phase 3 SOPHIA trial (n = 536;
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Recently, there has been increasing use of systemic therapies and chemotherapy to penetrate the blood-brain barrier (BBB) and the presence of efflux pumps along the BBB may be compromised in this setting. Therefore, mandatory for CNS activity because there is evidence that the BBB may be compromised in this setting. Despite advances in systemic therapy overall, the incidence of CNS relapses was similar in both arms of the KATHERINE trial (40% of relapses); the prevention of these relapses remains an unmet clinical need. However, in established BCBM, agent penetration across the intact BBB is not mandatory for CNS activity because there is evidence that the BBB may be compromised in this setting.97 This may be more relevant in the prevention of BCBM. The incidence of BCBM will likely increase as OS outcomes for HER2-positive MBC continue to improve; therefore, novel strategies to prevent and treat BCBM are a research priority. Many clinical trials historically excluded patients with active (or even stable) BCBM; the HER2CLIMB study established an important precedent by including patients with active BCBM when clinically appropriate.15 Treatment for HER2-positive CNS disease typically includes surgery for solitary lesions, stereotactic radiosurgery for patients with ≤4 BCBM, whole-brain radiation for multiple lesions, or a combined approach.15,96-98 Over the last decade, there has been increasing use of systemic therapy either in place of, or as an adjunct to, local therapy. Combinations evaluated to date include lapatinib and capecitabine; neratinib and capecitabine; tucatinib, trastuzumab, and capecitabine; and T-DM1 and intrathecal trastuzumab (leptomeningeal disease).15,99-104 The optimal CNS ORR observed (ie, volumetric reduction) was approximately 50%, in TBCRC 022 (ClinicalTrials.gov identifier NCT01494662) participants who received neratinib and capcitabine; the next cohort of this trial is evaluating the combination of neratinib and T-DM1.105 An overarching message is that consideration of the long-term side effects of systemic and locoregional therapy is very important because the median OS for patients with HER2-positive BCBM is now approximately 3 years.

Going forward, urgent improvements to the current standard of care are required. Innovation in drug development and clinical trial design is essential, including further studies of HER2-targeted TKIs, optimized HER2 monoclonal antibodies that cross the BBB effectively, trials focusing on brain metastasis prevention (ClinicalTrials.gov identifier NCT03190967), novel preclinical models, drug combinations, and therapeutic targets. The onus is on oncologists to enroll suitable patients on clinical trials, including those with progressive or untreated brain metastasis. Furthermore, thoughtful trial designs by experienced researchers incorporating appropriate CNS endpoints and relevant patient-reported outcomes are required.106

New Drugs and Treatment Strategies in HER2-Positive MBC

This section reviews emerging combination therapies in HER2-positive MBC, for which HER2 is not the target. There is good preclinical rationale and early-phase clinical trials to support the study of checkpoint inhibitors, CDK4/CDK6 inhibitors (CDK4i/CDK6i), and PIK3CA inhibitors (PIK3CAi) in this setting.76,88,107 Immunotherapy HER2-enriched (HER2-E) tumors are immunogenic; they have a higher mutational burden compared with luminal tumors, and approximately 50% are programmed death–ligand-1 (PD-L1) positive.108,109 Preclinical data were suggestive of a synergistic effect of antiprogrammed cell death protein 1 (anti–PD-1)/anti–PD-L1 agents with trastuzumab. Therefore, studies to determine the role of immunotherapy in HER2-positive MBC have been conducted. To date, clinically meaningful improvements in oncologic outcomes have not been noted, although research is ongoing.

PANACEA (ClinicalTrials.gov identifier NCT02129556) was a phase 1b/2 trial that evaluated treatment with pembrolizumab and trastuzumab in heavily pretreated patients with HER2-positive MBC.78 Response rates were modest; however, the ORR was superior in patients with PD-L1-positive disease (15%), which, in this trial, was defined as a combined positive score ≥1% (ie, the ratio of PD-L1–positive cells [tumor cells, lymphocytes, and macrophages] to the total
number of tumor cells \times 100\%). Pembrolizumab plus trastuzumab was safe and showed activity and durable clinical benefit in patients with PD-L1-positive, trastuzumab-resistant, HER2-positive MBC. It was therefore concluded that further studies should focus on less heavily pretreated, PD-L1-positive patients. The phase 2 KATE2 trial (ClinicalTrials.gov identifier NCT02924883) randomized participants with HER2-positive MBC to receive T-DM1 and atezolizumab or placebo. Atezolizumab and T-DM1 did not demonstrate a clinically significant PFS advantage compared with the control arm, although numerically higher PFS and ORR were noted in PD-L1-positive patients who were treated with atezolizumab.\textsuperscript{76} Although a numerically higher incidence of SAEs was noted in the atezolizumab arm, rates of grade 3 through 5 AEs were similar. Currently, the phase 3 NRG-BR004 trial (ClinicalTrials.gov identifier NCT0319988) is randomizing 600 patients with newly diagnosed, HER2-positive MBC (unselected for PD-L1 status) to receive paclitaxel, trastuzumab, and pertuzumab plus atezolizumab or placebo. The primary endpoint is PFS, and numerous secondary and correlation objectives will also be evaluated.

**Anti-HER2–mTOR/PI3K inhibitor combinations**

PI3KCA mutations occur in 25% to 30% of HER2-positive MBCs.\textsuperscript{110} Previous trials of the mTOR inhibitor everolimus and the pan-PI3K inhibitor (PI3Ki) buparlisib were associated with unclear clinical benefit and/or unacceptable toxicity.\textsuperscript{111,112} The advent of less toxic, α-specific PI3K inhibitors has renewed interest in evaluating PI3Ki in combination with HER2-directed therapies. In a phase 1 study, the combination of alpelisib and T-DM1 was tolerable and active in trastuzumab-resistant, HER2-positive MBC, with an ORR of 43% (n = 14) and a median PFS of 8.1 months; the dose-limiting toxicity was rash.\textsuperscript{88} Ongoing trials of PI3Ki in combination with HER2-directed therapy for the first-line treatment of HER2-positive MBC include 2 clinical trials (ClinicalTrials.gov identifiers NCT04208178 and NCT04108858), both of which are evaluating the benefit of adding a PI3Ki to maintenance trastuzumab and pertuzumab after induction therapy with a taxane, trastuzumab, and pertuzumab.

**CDK4/CDK6 inhibitors**

Deregulation of the CDK4/CDK6–D-type–Rb pathway has been observed in several cancers, which led to the development of CDK4i/CDK6i to induce G1 arrest and apoptosis.\textsuperscript{113,114} Targeting CDK4/CDK6 kinases in HER2-positive BC is attractive because they are downstream of HER2 and many of the processes promoting resistance to HER2-directed therapies.\textsuperscript{115} On the basis of encouraging phase 1 data, further clinical development ensued in the HER2-positive space.\textsuperscript{116} monarcHER (n = 237; ClinicalTrials.gov identifier NCT02675231) was a randomized phase 2 trial in which participants with pretreated, HR-positive, HER2-positive MBC were randomized to trastuzumab with investigator’s choice of chemotherapy; trastuzumab and abemaciclib; or trastuzumab, abemaciclib, and fulvestrant.\textsuperscript{86} The median PFS was superior in the trastuzumab, abemaciclib, and fulvestrant arm compared with the trastuzumab and chemotherapy arm (8.3 months vs 5.7 months; \(P = .0253\)). Abemaciclib will be evaluated further in HER2-positive EBC and MBC (eg, ClinicalTrials.gov identifier NCT03846583). The Academic and Community Cancer Research United trial ACCRU-BR-1801 (ClinicalTrials.gov identifier NCT04351230) is a phase 2 study that will evaluate PFS in patients with HER2-positive MBC who progressed on a taxane, trastuzumab, and pertuzumab and who are randomized to receive T-DM1 with or without abemaciclib. The PATRICIA trial (ClinicalTrials.gov identifier NCT02448420)\textsuperscript{117} is randomizing postmenopausal women with HR-positive, HER2-positive MBC who received 1 to 4 prior lines of HER2-targeted therapy to trastuzumab, palbociclib, and endocrine therapy or to trastuzumab and physicians’ choice of chemotherapy or T-DM1. Finally, the phase 3 PATINA trial (ClinicalTrials.gov identifier NCT02947685) is investigating the addition of palbociclib or placebo to maintenance therapy with trastuzumab, pertuzumab, and endocrine therapy after 4 to 8 cycles of induction chemotherapy and HER2-directed therapy in the first-line metastatic setting.\textsuperscript{107}

**Challenges Associated With HER2-Directed Therapy**

**Mechanisms of Resistance to HER2-Directed Therapy and Strategies to Predict Response to Treatment**

One of many challenges associated with HER2-directed therapy is de novo or acquired resistance to these therapies.\textsuperscript{9,88} Acquired resistance in HER2-positive MBC is a particularly difficult challenge because tumor cells preferentially survive in response to prior HER2-directed therapies. Increasing our knowledge regarding the mechanisms of resistance enables researchers to develop better treatments for these patients. Identifying predictive biomarkers of response to treatment assists oncologists to tailor therapy effectively for patients. Examples of resistance mechanisms to trastuzumab include incomplete blockade of the HER2-receptor, which activates compensatory mechanisms within the HER family (eg, HER3),\textsuperscript{119} activation of alternative receptor tyrosine kinases (IGF-1R, MET),\textsuperscript{119,120} hyperactivation of the HER2 downstream signaling cascade (the PI3K/AKT/mTOR pathway),\textsuperscript{110} and the suppression of tumor-suppressor genes (PTEN).\textsuperscript{121} The activation of other downstream signaling cascades involved in tumorigenesis includes bidirectional crosstalk between ER and HER2\textsuperscript{122,124} and the cyclin D1–CDK4/Rb axis.\textsuperscript{125} A more detailed discussion of the mechanisms associated with resistance to
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Despite extensive efforts to discover predictive biomarkers of response to HER2-directed therapy, currently, HER2 status is the only established biomarker. However, variations in HER2 itself, such as HER2 mRNA or protein levels, HER2 gene copy numbers, and mutations in HER2 that result in decreased binding of HER2-directed targets (eg, a truncation in the HER2 receptor p95HER2), can contribute to acquired resistance. In addition, other potential biomarkers have been evaluated, including HER2 coligands (HER3, EGFR, IGFR), downstream pathways (PIK3CA), stromal components (tumor-infiltrating lymphocytes [TILs]), and host factors (FCγR polymorphisms). Unfortunately, the clinical significance of these biomarkers in helping to tailor therapy is limited by small study sizes, requiring further validation; therefore, most of the studies to date are merely hypothesis generation. In particular, retrospective analyses of patient biospecimens from the CLEOPATRA, EMILIA, and TH3RESA (ClinicalTrials.gov identifier NCT01419197) trials, among others, have been largely uninformative, although these results should aid in hypothesis generation for future studies on prognostic biomarkers.

The Neo AL TTO (ClinicalTrials.gov identifier NCT00553358) and the German Breast Group trials demonstrated that distinct genes or pathway-level DNA alterations are predictive of responses to HER2-directed therapy. In CALGB 40601, integrated DNA and RNA analyses concluded that there was an independent association between copy number alterations and pCR rates when the investigators accounted for the RNA expression signature subtype. Liquid biopsies (eg, circulating tumor DNA [ctDNA]) have the potential to capture a more accurate picture of the dynamic and heterogeneous cancer genome in a minimally invasive manner compared with tumor biopsies. The MutHER trial (ClinicalTrials.gov identifier NCT03289039) evaluated the efficacy of neratinib in 16 patients with advanced, HER2-negative BC and somatic HER2 mutations. It should be noted that somatic mutations in HER2 occur in approximately 3% of BCs, mainly in the HR-positive, HER2-negative subtype. HER2 mutations represent a targetable BC subset; sensitivity to irreversible HER kinase inhibition appears to be influenced by the presence of concurrent, activating genomic events in the pathway. Serial ctDNA analyses were performed on 14 of 16 patients (at baseline, at 4 weeks, and at disease progression). Eleven patients possessed the same HER2 mutation in both tissue and ctDNA at baseline, which suggests that ctDNA may be a beneficial noninvasive study to detect HER2 mutations. Importantly, a reduction in the variant allele fraction of HER2-mutated DNA at 4 weeks was associated with drug efficacy and PFS (Spearman correlation coefficient, −0.69; P = .017); conversely, there was an association between an increase in the variant allele fraction and disease progression, because all patients experienced an increased variant allele fraction before progression. In a phase 1 study evaluating the pan-HER2 inhibitor pyrotinib for patients with advanced, HER2-positive BC, it was noted that PIK3CA and TP53 mutations in ctDNA, but not in tumor tissue, were predictive of treatment response. Taken together, these findings indicate that ctDNA may be an important, minimally invasive tool to advance biomarker-based research in advanced BC.

The centrality of the immune microenvironment in determining response to therapy and oncologic outcomes is increasingly acknowledged. Several studies have evaluated the prognostic impact of activated immune cells in the tumor microenvironment of HER2-positive BC; both TILs and activated immune signatures are associated with superior pCR rates and event-free survival outcomes, and these findings are independent of tumor-associated features. Studying TILs and activated immune signatures may be a useful approach to evaluate de-escalation strategies by identifying patients with highly responsive disease and may serve a role in determining efficacy to checkpoint inhibitors, as previously discussed. Furthermore, in the landmark CLEOPATRA trial, increased stromal TILs were significantly associated with an improved OS in patients with advanced, HER2-positive BC who received docetaxel, trastuzumab, and pertuzumab or placebo, which may have implications for the utility of immune checkpoint activity in this setting. Going forward, the use of TILs as a stratification factor in clinical trials could help to determine whether therapies that enhance immunity further improve OS in HER2-positive MBC.

Intrinsic Subtyping and Response to Treatment

BC is comprised of 5 intrinsic molecular subtypes (eg, luminal A, luminal B, HER2-E, basal-like, and normal-like), which can influence response to treatment. In the preoperative CALGB 40601 and Neo AL TTO studies, correlative analyses noted considerable intertumoral heterogeneity with respect to tumor genomics and the tumor microenvironment, both of which had a significant impact on pCR rates (this was not a preplanned analysis). In CALGB 40601, Neo AL TTO, and the phase 2 neoadjuvant PAMELA study (ClinicalTrials.gov identifier NCT01973660), the molecular profile and heterogeneity of HER2-positive breast tumors in response to dual HER2-directed therapy with trastuzumab and lapatinib were studied. Several intrinsic subtypes (luminal A and luminal B, HER2-E) were found to be independent factors in determining the
likelihood of obtaining a pCR when HR status was excluded from the analysis. Positive predictors of a pCR included the presence of a chromosome 6p amplification, a TP53 mutation, the HER2-E subtype, and distinct immune signatures, whereas factors associated with a decreased likelihood of pCR included the ER-positive and luminal subtypes, respectively. Therefore, patients with HER2-E disease who achieve a pCR on dual HER2-directed therapy may be candidates for a de-escalated chemotherapy regimen, although further validation is required before these biomarkers can be used for therapeutic de-escalation.

### Novel Imaging Modalities

The utility of tumor biopsies in patients with HER2-positive BC has been hindered by the heterogeneity of HER2 overexpression. By evaluating radioisotopes (eg, zirconium-89 [89Zr] and indium-111 [111In]) for single-photon emission CT (SPECT), which accumulate in HER2-overexpressing malignancies, functional imaging aims to perform a whole-body assessment of HER2 status and predict response to treatment. The ZEPHIR trial (ClinicalTrials.gov identifier NCT01565200) evaluated 89Zr-trastuzumab (HER2-PET) and early serial FDG-PET/CT imaging in patients with advanced, HER2-positive BC who were receiving systemic therapy with T-DM1. Notably, patients who had negative HER2-PET results and stable disease (eg, no evidence of radiographic progression) or metabolic progression after the first cycle of T-DM1 did not respond to subsequent treatment (eg, negative predictive value, 100%). Furthermore, the combination of baseline HER2-PET/CT and FDG-PET/CT imaging accurately predicted the time to treatment failure. Therefore, additional research evaluating functional imaging in advanced, HER2-positive BC is warranted because this approach may assist oncologists in predicting the response to treatment and tailoring therapy accordingly.

### Conclusions

Undeniably, major progress has been made in the management of patients with early and advanced-stage, HER2-positive BC over the past 2 decades. However, primary or acquired resistance to therapy remains a vexing problem, and a study of compounds that may inhibit HER2 signaling more effectively is currently in progress (eg, novel HER2-targeted TKIs, monoclonal antibodies, ADCs, and others). At the time of this writing, there have been 3 recent FDA approvals in the metastatic setting, and further approvals may follow shortly. Furthermore, regimens incorporating HER2-directed therapy in combination with CDK4i/CD6i, PI3Ki, and immunotherapy may supersede therapeutic resistance in some cases and may have implications for treatment sequencing in the metastatic setting. A major challenge in the field relates to effectively tailoring therapy in early-stage and advanced-stage disease. Harnessing the potential of functional imaging and identifying predictive biomarkers of response to therapy will be essential to ensure continued improvements in this regard. Finally, the management of HER2-positive brain metastasis is a major challenge, and innovations in research involving drug development and clinical trial design are urgently needed. Overall, however, the outlook for patients with early and advanced-stage, HER2-positive BC has dramatically improved since the inception of HER2-targeted therapy. Hopefully, novel research strategies addressing the challenges described above will further enhance treatment options for our current and future patients.

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