HER2-Positive Metastatic Breast Cancer: A Comprehensive Review

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Abstract: Cases of human epidermal growth factor receptor 2 (HER2)–positive breast cancer represent approximately 15% to 20% of all breast cancers. Historically, this subtype of breast cancer was associated with an increased risk for the development of systemic and brain metastases and poor overall survival. The introduction of trastuzumab dramatically changed the outcomes of patients with HER2-positive disease, with many demonstrating outcomes similar to those of patients with luminal tumors. Currently, the first-line standard of care for patients with HER2-positive metastatic breast cancer is dual HER2 antibody therapy with pertuzumab/trastuzumab plus a taxane. After progression, the standard of care is trastuzumab emtansine (T-DM1). Although the treatment choices for patients whose disease has progressed on these agents are more limited, promising new drugs have emerged as effective options, including tucatinib and trastuzumab deruxtecan, which were recently approved by the US Food and Drug Administration. Finding the best treatment sequencing for each patient, developing reliable predictive biomarkers, and understanding the mechanisms of resistance to these drugs are necessary to maximize patient outcomes and quality of life. In this review, we analyze the management strategies for metastatic HER2-positive breast cancer, address specific situations, such as the treatment of patients with brain metastases, and discuss future directions in the treatment of this subtype.

Keywords
HER2-positive, metastatic breast cancer

Introduction

Amplification of the human epidermal growth factor receptor 2 gene (*HER2*) is present in approximately 15% to 20% of breast cancers and has been associated with an increased risk for the development of systemic metastasis and poor survival.[1,2] The introduction of anti-HER2 agents has changed the treatment paradigm for HER2-positive breast cancer in the last 2 decades, and the development of many drugs has led to unprecedented survival outcomes. Monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADCs) are now the backbone of the treatment of HER2-positive

Table 1. Pivotal Trials of FDA-Approved Agents for HER2-Positive Metastatic Breast Cancer

Drug	Pivotal Study	Treatment Line	Arms	OS Increment, mo	PFS Increment, mo	HR
Antibodies						
Trastuzumab	H0468g[3]	1	Arm A: AC or paclitaxel + trastuzumab Arm B: AC or paclitaxel	4.8	2.8	0.80 for OS 95% CI, 0.64-1.00; *P*=.042
Pertuzumab	CLEOPATRA[4]	1	Arm A: docetaxel + trastuzumab + pertuzumab Arm B: docetaxel + trastuzumab + placebo	16.3	66.3	0.68 for OS 95% CI, 0.56-0.84; *P*<.001
Tyrosine kinase inhibitors						
Lapatinib	EGF100151[5]	2	Arm A: capecitabine + lapatinib Arm B: capecitabine	NS	1.9	HR, 0.55 for PFS 95% CI, 0.40-0.74; *P*<.001
Neratinib	NALA[6]	3	Arm A: capecitabine + neratinib Arm B: capecitabine + lapatinib	NS	2.2	HR, 0.76 for PFS 95% CI, 0.63-0.93; *P*=.0059
Tucatinib	HER2CLIMB[7]	3	Arm A: capecitabine + trastuzumab + tucatinib Arm B: capecitabine + trastuzumab + placebo	4.5	2.2	HR, 0.66 for OS 95% CI, 0.50-0.88; *P*=.005
Antibody-drug conjugates						
T-DM1	EMILIA[8]	2	Arm A: T-DM1 Arm B: capecitabine + lapatinib	5.8	3.2	HR, 0.68 for OS 95% CI, 0.55-0.85; *P*<.001
Trastuzumab deruxtecan	DESTINY-Breast01[9]	>2	Single arm	NA	NA	NA

AC, doxorubicin plus cyclophosphamide; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mo, months; NA, not applicable; NS, not significant; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

metastatic breast cancer (MBC); however, defining the best sequencing of treatment and understanding resistance mechanisms remain a challenge. Here, we review the possible approaches to the treatment of advanced HER2-positive breast cancer, which are based on data from the main pivotal clinical trials (Table 1).[3-9]

First-line Treatment With Trastuzumab, Pertuzumab, and Taxanes

In the early 2000s, combining trastuzumab with chemotherapy significantly improved progression-free survival (PFS) and overall survival (OS) among patients with HER2-positive metastatic breast cancer (MBC). Trastuzumab binds to subdomain IV of the HER2 extracellular domain, inhibiting the homodimerization that activates the intracellular signaling pathway and preventing cell proliferation and survival.[10] The addition of trastuzumab to chemotherapy—an anthracycline plus cyclophosphamide (AC) or paclitaxel—vs chemotherapy alone increased PFS (7.4 vs 4.6 months; *P*<.001), the objective response rate (ORR; 50% vs 32%; *P*<.001), and OS (25.1 vs 20 months; *P*=.046).[3] Cardiac dysfunction was the most significant toxicity associated with the addition of trastuzumab, with an incidence of 13% to 27% and a discontinuation rate of 8%. Of note, because the anthracycline combination with trastuzumab demonstrated a high incidence of cardiac dysfunction, the concomitant use of AC plus trastuzumab has been abandoned, and the combination of single-agent, non-anthracycline chemotherapy with anti-HER2 therapy has been widely adopted in the metastatic setting.

Pertuzumab (Perjeta, Genentech), a second-generation anti-HER2 antibody, binds to subdomain II of the HER2 transmembrane receptor. This blockade prevents the heterodimerization of HER2 with the HER3 receptor,

suppressing the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways.[11] The CLEOPATRA trial[12] evaluated the addition of pertuzumab to trastuzumab and a taxane. Patients were randomly assigned to receive either pertuzumab or placebo plus trastuzumab plus docetaxel. After a median follow-up of 99.9 months, an outstanding improvement of 16.3 months (median OS, 57.1 months in the pertuzumab group vs 40.8 months in the control group) was observed with the addition of pertuzumab, a magnitude of gain in absolute OS that is rarely seen. The risk for death decreased by 31%. This benefit was consistent in all prespecified subgroups and was maintained when patients crossed over. Median PFS also improved in patients in the pertuzumab group (18.7 months in the pertuzumab group vs 12.4 months in the control group; hazard ratio [HR], 0.68; 95% CI, 0.58-0.80; *P*<.001). Overall, pertuzumab was well tolerated, but the rates of diarrhea, rash, headache, and muscle spasm were higher than in the trastuzumab-alone group. No difference in cardiotoxicity was observed between the arms.[4,13] These data established trastuzumab, pertuzumab, and a taxane as the standard first-line treatment in patients with HER2-positive MBC.

Tyrosine Kinase Inhibitors

TKIs are another class of anti-HER2 drug that act intracellularly, inhibiting cellular growth by stopping transduction cascades. Currently, the US Food and Drug Administration (FDA) has approved 3 TKIs for the treatment of HER2-positive MBC: lapatinib, neratinib (Nerlynx, Puma), and tucatinib (Tukysa, Seattle Genetics).

Lapatinib

Lapatinib inhibits HER2 and epidermal growth factor receptor type 1 (EGFR1). It was the first TKI approved by the FDA for the treatment of HER2-positive MBC. EGF100151[5] was a phase 3 trial that was terminated early after preliminary analysis demonstrated a significant improvement in PFS from 4.3 to 6.2 months in patients who received the combination of lapatinib plus capecitabine compared with those who received capecitabine alone (HR, 0.55; 95% CI, 0.40-0.74; *P*< 0.001). Although a trend was noted toward increased OS (75.0 weeks for the combination arm vs 64.7 weeks for the monotherapy arm [HR, 0.87; 95% CI, 0.71-1.08; *P*=.210]), no statistically significant benefit was observed. The EGF104900 study has demonstrated a benefit of continuing trastuzumab beyond progression when given with lapatinib. This phase 3 trial randomly assigned patients to trastuzumab plus lapatinib vs lapatinib alone. Median PFS was 11.1 weeks in the combination arm vs 8.1 weeks in the lapatinib arm (HR, 0.74; 95% CI, 0.58-0.94; *P*=.011). Median OS was also superior with trastuzumab plus lapatinib vs lapatinib alone (14 months vs 9.5 months; HR, 0.74; 95% CI, 0.57-0.97; *P*=.026).[14]

Lapatinib either as monotherapy or in combination was associated with several grade 3 adverse events, mainly diarrhea (12%), nausea (2%), vomiting (2%) and hand-foot syndrome (7%) (Table 2).

Neratinib

Neratinib, an irreversible pan-HER inhibitor (HER1, HER2, and HER4), was initially approved by the FDA for adjuvant therapy on the basis of the EXTENET trial.[15] Recently, the FDA granted approval for the use of neratinib in the metastatic setting as third-line therapy on the basis of results of the NALA trial.[6] In this phase 3 trial, patients who had previously received 2 lines of anti-HER2 therapy were randomly assigned to receive capecitabine plus neratinib or capecitabine plus lapatinib. After a median follow-up of 29.9 months, the patients who received neratinib demonstrated significantly better PFS, with a 2.2-month absolute difference, when compared with those who received lapatinib (HR, 0.76; 95% CI, 0.63-0.93; *P*=.0059). No statistically significant difference in OS between the arms was observed (HR, 0.88; 95% CI, 0.72-1.07; *P*=.2086). A subgroup analysis showed that PFS was significantly longer among patients with hormone receptor–negative disease treated with neratinib than among patients with estrogen receptor (ER)–positive disease treated with lapatinib (*P*<.001). In addition, patients with nonvisceral disease had significantly longer PFS and OS with neratinib plus capecitabine than with lapatinib plus capecitabine. No difference in ORR was observed between the arms. Although the patients who received neratinib had a higher incidence of grade 3 diarrhea (24.4% vs 12.5%), quality-of-life scores were similar.

Tucatinib

Tucatinib is a new TKI that is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR. In vitro studies showed that tucatinib is approximately 500-fold more selective for HER2 vs EGFR, which explains its favorable toxicity profile.[16] Additionally, its small molecular size facilitates crossing the brain-blood barrier, allowing direct activity against central nervous system (CNS) disease.[17] In 2 initial phase 1 trials,[17,18] tucatinib demonstrated promising antitumor activity with a tolerable adverse events profile.

HER2CLIMB[7] is a placebo-controlled phase 3 trial that evaluated tucatinib in combination with trastuzumab and capecitabine as third-line therapy in patients previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1; Kadcyla, Genentech). Patients were randomly assigned to receive either tucatinib or placebo in combination with trastuzumab and capecitabine. The primary endpoint was PFS, and secondary endpoints

Table 2. Incidence (%) of the Most Clinically Relevant Grade 3 Adverse Events Associated With Approved Anti-HER2 Drugs

Adverse Event	Trastuzumab[a]	Pertuzumab[b]	T-DM1	T-Dx	Tucatinib[b]	Neratinib[a]	Lapatinib[a]
Anemia	3.5	2.5	2.7	8.2	3.7	2.0	1.6
Neutropenia	45.8	45.9	2.0	19.6	2.2	NR	4.3
Thrombocytopenia	NR	NR	12.9	3.8	NR	NR	0.2
Fatigue	3.3	2.2	2.4	6.0	4.7	3.0	3.5
Diarrhea	5.0	7.9	1.6	2.7	12.9	24.4	12
Ventricular systolic dysfunction	2.8	1.2	0.2	0.5	NR	4.3	0
Vomiting	5	NR	0.8	4.3	3.0	4.0	2
Elevated ALT	NR	NR	2.9	1.6	5.4	NR	1.4
Elevated AST	NR	NR	4.3	1.6	4.5	NR	0.8
Hand-foot syndrome	NR	NR	0	NR	13.1	9.6	7
Pneumonitis	NR	NR	NR	0.5	NR	NR	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HER2, human epidermal growth factor receptor 2; NR, not reported; T-DM1, trastuzumab emtansine; T-Dx, trastuzumab deruxtecan.

[a] Plus chemotherapy.

[b] Plus chemotherapy and trastuzumab.

were OS, ORR, and safety. Of note, in this unique trial design, patients with active and treated brain metastasis were included in the study (approximately 45% in both arms) and were permitted to continue the treatment after exclusively local progression following local therapy.

After a median follow-up of 14 months, the median PFS was 7.8 months in the tucatinib arm vs 5.6 months in the placebo arm, with a 46% decrease in risk for death or progression (HR, 0.54; 95% CI, 0.42-0.71; *P*<.001).[7] Tucatinib was superior across all analyzed subgroups regardless of metastasis site and hormone receptor status. The median OS was 21.9 months in the tucatinib arm vs 17.4 months in the placebo arm (HR, 0.66; 95% CI, 0.50-0.88; *P*=.005). As a third-line agent, tucatinib impressively doubled the ORR compared with placebo (40.6% vs 22.8%; *P*<.001). Diarrhea, transaminitis, and hand-foot syndrome of any grade were more frequent in the tucatinib arm, but only a small number of patients had grade 3 or higher adverse events (Table 2). Increases in the serum creatinine level were observed in 13.9% of the patients in the tucatinib arm, but this alteration was caused by changes in creatinine transporters, preserving glomerular filtration.

These data suggest that the combination of capecitabine plus tucatinib and trastuzumab is a highly effective option, with an impressive 4-month increase in OS in heavily pretreated patients, including those with brain metastasis. The findings led to FDA approval for the treatment of patients with advanced HER2-positive disease who had received 1 or more prior anti-HER2–based regimens in the metastatic setting. This unprecedented indication allows clinicians to choose the best option for the second-line treatment of each patient—either T-DM1 or tucatinib/capecitabine/trastuzumab (Figure).[7]

Antibody-Drug Conjugates

ADCs are a new class of anticancer drugs that deliver cytotoxic chemotherapy directly into a tumor cell via linkage to a specific targeted antibody.[19]

T-DM1

T-DM1 consists of trastuzumab covalently linked via a noncleavable linker to the cytotoxic agent DM1 (emtansine, a potent microtubule inhibitor); the aim is to deliver DM1 into tumor cells while retaining the antitumor activity of trastuzumab.[20] The efficacy of T-DM1 was demonstrated in 3 phase 2 trials of previously treated patients with HER2-positive breast cancer.[21-23] The pivotal phase 3 EMILIA trial[8] compared T-DM1 with lapatinib plus capecitabine as second-line treatment in patients with HER2-positive breast cancer previously treated with trastuzumab and a taxane. Co-primary endpoints were PFS, OS, and safety; secondary endpoints included ORR, duration of response, and time to symptom progression. Patients with untreated brain metastasis were not included.

Treatment with T-DM1 improved median PFS (9.6 vs 6.4 months) compared with lapatinib plus capecitabine, decreasing the chance of death or disease progression in 35% of patients (95% CI, 0.55-0.77; *P*<.001). With a higher ORR (43% in the T-DM1 arm vs 30% in the lapatinib-plus-capecitabine arm) and a better adverse event profile, T-DM1 was associated with a better quality of life compared with lapatinib plus capecitabine. T-DM1 also significantly increased OS (30.9 vs 25.1 months; HR, 0.68; 95% CI, 0.55-0.85; *P*<.001). This benefit was observed across all subgroups, regardless of hormone receptor status and site of metastatic disease.

TH3RESA, another phase 3 trial,[24] has also shown improved PFS and OS with T-DM1 in patients with HER2-positive breast cancer who have been exposed to 2 anti-HER2 lines of therapy, including trastuzumab and lapatinib, in comparison with physician choice of treatment. These findings led to FDA approval of T-DM1 for the second- and third-line treatment of patients who previously received trastuzumab and a taxane.

The MARIANNE study[25] failed to establish T-DM1 as a good option in treatment-naive patients. This study randomly assigned patients to receive trastuzumab plus a taxane (arm 1), T-DM1 plus placebo (arm 2), or T-DM1 plus pertuzumab (arm 3). No statistically significant differences in PFS were observed among the arms, with median PFS values of 13.7, 14.1, and 15.2 months in arms 1, 2, and 3, respectively. Similarly, no difference was observed across hormone receptor subgroups. Adverse events profiles and quality of life were better in the T-DM1 arms than in the trastuzumab/taxane arm. On the basis of these data, T-DM1 is considered the standard second-line treatment in patients with HER2-positive disease that progressed on taxane-based therapy plus dual blockade with trastuzumab and pertuzumab.

Trastuzumab Deruxtecan

Trastuzumab deruxtecan (Enhertu, Daiichi-Sankyo/AstraZeneca), which has an 8-fold higher drug-to-antibody ratio compared with T-DM1, is composed of a humanized monoclonal antibody specifically targeting HER2 linked to a topoisomerase I inhibitor via a cleavable linker. Interestingly, the composition of this drug favors a high level of stability when it is free in plasma, but it is easily cleaved by enzymes that are overexpressed on the tumor cell surface. Trastuzumab deruxtecan is also active against cells with a low level of HER2-expression owing to the high level of membrane permeability of the payload, which allows this cytotoxic element to cross the cellular membrane and act directly against neighboring cells regardless of their level of HER2 expression, a phenomenon called the bystander effect.[26-30]

DS8201-A-J101[31] was a 2-part phase 1 trial that showed promising results not only in tumors with HER2 overexpression but also in tumors with score 1+ or 2+ expression on immunohistochemistry (IHC) analysis and no amplification on fluorescence in situ hybridization (FISH). In the second part of this large phase 1 trial, patients received trastuzumab deruxtecan every 3 weeks, and the primary endpoints were safety and ORR. A total of 115 patients who had previously received T-DM1 and trastuzumab were able to receive at least 1 dose of DS8201, and the safety analysis demonstrated a manageable adverse events profile, with most grade 3 events being hematologic. The rate of discontinuation due to drug-related adverse events was 11%. Two patients (2%) died owing to drug-related interstitial lung disease (ILD). No cases of decreased cardiac function were observed. Among 111 patients with measurable disease, an objective response was achieved in 59.5% and confirmed disease control (ORR or stable disease) was achieved in 93.7%. Similar findings were observed in patients who had also previously received pertuzumab (86%), with an ORR of 62.5% and a disease control rate of 93.8%.

The DESTINY-Breast01 study[9] was a pivotal multicenter, open-label phase 2 study that led to FDA approval of trastuzumab deruxtecan for patients with HER2-positive MBC after progression on T-DM1. Patients with active or untreated brain disease were excluded. The median number of previous lines of systemic treatment was 6 (range, 2-27), all patients had previously received trastuzumab and T-DM1, and 65% had previously received pertuzumab. Among the 184 patients who received trastuzumab deruxtecan, a response rate of 60.9% was observed (6% had a complete response and 54.9% had a partial response). The disease control rate was impressive, at 97.3%. Similar findings of a response rate of approximately 60% were observed across subgroups defined by previous treatment with pertuzumab, hormonal receptor status, and recent progression to T-DM1. Long-term outcomes were also impressive. The duration of response was 14.8 months, the median PFS was 16.4 months, and the estimated OS was 93.9% at 6 months and 86.2% at 12 months. As with DS8201-A-J101, gastrointestinal and hematologic toxic effects were the most common and manageable adverse events, but a high incidence of ILD was observed (13.6% [0.5% grade 4]). Table 2 shows the most significant adverse events. Given the potential risk for ILD, careful monitoring is recommended for all patients receiving trastuzumab deruxtecan, and drug discontinuation is recommended for anyone with grade 2 or higher toxicity.

Powell and colleagues[32] recently showed that Japanese ancestry (odds ratio [OR], 3.6; 95% CI, 2.1-6.1; *P*<.001) and the breast as the primary tumor site (OR, 2.5; 95% CI, 1.2-5.0; *P*=.01) conferred an increased risk for trastuzumab

deruxtecan–induced ILD. Moderate impairment of renal function also showed a trend toward increased risk for ILD (OR, 2.0; 95% CI, 1.07-3.71; *P*=.028).

Special Conditions

Brain Metastasis

Despite major therapeutic advances in the management of patients with HER2-positive MBC, CNS metastases will develop in 30% to 55% of patients.[33] In this context, the development of new drugs that cross the blood-brain barrier, as well as clinical trial designs that include patients with active CNS metastases, remain crucial.

Tucatinib is the newest treatment strategy for active brain metastases in HER2-positive MBC. An objective intracranial response with tucatinib plus trastuzumab was demonstrated in patients previously exposed to neratinib or lapatinib in 2 phase 1b trials.[34,35] The unique design of the HER2CLIMB trial has allowed the participation of patients with untreated or recently progressed CNS disease, as well as patients who have isolated CNS progression during study treatment. Lin and colleagues[36] performed an exploratory analysis focusing exclusively on intracranial and OS outcomes in patients with CNS disease. Patients were classified in 3 different groups according to CNS disease status: treated and stable (117 patients), treated and progressing (108 patients), and untreated (66 patients). In the 291 patients with brain metastasis, an impressive difference was observed between the arms, with 40.2% of patients in the tucatinib arm alive or free of CNS progression vs no patients in the placebo arm within 1 year (HR, 0.32; 95% CI, 0.22-0.48; *P*=.0001). OS was also better in the patients with CNS disease who received tucatinib than in those who received placebo. Median OS was 18.1 months in the tucatinib arm vs 12.0 months in the control arm (HR, 0.58; 95% CI, 0.40-0.85; *P*=.005). This result was observed not only in patients with active brain metastasis (treated and progressing or untreated [174 patients]) but also in patients with stable CNS disease (117 patients). The intracranial ORR was 47.3% in the tucatinib arm vs 20.0% in the control arm (*P*=.03).

Of note, this is the first randomized study to demonstrate clinically meaningful improvement in patients with active or treated CNS disease. The ongoing HER2CLIMB-02 trial is a randomized, double-blind, placebo-controlled phase 3 study to evaluate efficacy and safety of tucatinib plus T-DM1 that allows the enrollment of patients with active and untreated CNS metastasis.[37]

Neratinib has also demonstrated activity in brain metastases. Of the patients in the NALA trial,[6] 16% had asymptomatic or stable CNS brain metastases (treated or untreated), and fewer patients in the neratinib arm required a new intervention in CNS metastases. This finding is similar to reported results from the phase 2 NEfERT-T trial,[38] which compared neratinib combined with paclitaxel in the first-line setting with paclitaxel plus trastuzumab. The primary endpoint, PFS, was similar in the 2 arms (*P*=.89), and the neratinib arm had more grade 3/4 adverse events. The secondary endpoint, however, which evaluated CNS recurrence, was significantly better in the patients who received neratinib plus paclitaxel. The incidence of CNS recurrence was 8.3% in the neratinib arm vs 17.3% in the trastuzumab arm (relative risk, 0.48; *P*=.002). Another interesting single-arm, multicohort phase 2 trial, TBCRC 022,[39] which evaluated the activity of neratinib plus capecitabine exclusively in patients with active brain metastases, demonstrated a substantial CNS ORR of 49% in lapatinib-naive patients and a CNS ORR of 33% in patients previously treated with lapatinib. The combination of neratinib and T-DM1 in active brain metastasis is being evaluated in an ongoing cohort of this study (NCT01494662).

Although CNS penetration seems to be limited with antibody-based agents, recent data on T-DM1 have shown activity in brain metastasis. In a retrospective exploratory analysis of EMILIA by Krop and colleagues,[40] the incidence of new brain metastases in patients without previous CNS disease was higher in those who received T-DM1 than in those who received lapatinib plus capecitabine (2.0% vs 0.7%). Among 95 patients with brain metastasis at baseline, 22.2% in the lapatinib arm showed local progression vs 16.0% in the T-DM1 group. OS was superior in the patients who received T-DM1 (HR, 0.38; 95% CI, 0.18-0.80; *P*=.008). Similarly, an exploratory analysis of the KAMILLA trial, an ongoing phase 3b study evaluating the safety and efficacy of T-DM1 in patients with HER2-positive MBC, has demonstrated an overall intracranial response rate of 42%.[41]

A subgroup analysis of patients with CNS metastases at baseline in DESTINY-Breast01 has been recently reported. In the 13% of the patients who had stable or treated brain metastasis, outcomes were similar to those of patients without CNS disease, with a median PFS of 18.1 months and ORR of 58.3%.[42] The DEBBRAH trial is a phase 2 trial that will test trastuzumab deruxtecan exclusively in patients with CNS disease (NCT04420598). However, data on trastuzumab deruxtecan in patients with active brain metastases are still lacking.

HER2-Positive/Estrogen Receptor–Positive Tumors

Approximately 50% of HER2-positive breast cancers also express hormone receptors. Preclinical evidence suggests that crosstalk between HER2 and estrogen receptor (ER) signaling pathways in breast cancer contributes to resistance to hormonal therapy. Clinical trial data confirm this

finding and show that trastuzumab combined with tamoxifen or fulvestrant restores tumor sensitivity to these hormonal agents. Although the ELECTRA[43] and TANDEM[44] phase 3 trials showed disappointing results for the use of trastuzumab plus aromatase inhibitors, the combination of dual anti-HER2 therapy plus aromatase inhibitors seems to achieve more satisfactory survival benefits.

The PERTAIN trial[45] randomly assigned patients to receive pertuzumab/trastuzumab combined with either anastrozole or letrozole or to receive trastuzumab plus an aromatase inhibitor after an optional induction chemotherapy phase. The combination of pertuzumab and trastuzumab significantly improved PFS compared with trastuzumab alone (18.9 vs 15.8 months; HR, 0.65; 95% CI, 0.48-0.89; *P*=.0070); however, this benefit was lost in the subgroup of patients who received induction chemotherapy. ORRs and clinical benefit rates were similar in the 2 arms. Although gastrointestinal adverse events were more frequent in the pertuzumab/trastuzumab arm, quality of life was better in this arm.

Updated results of the ALTERNATIVE trial[46] confirmed that an aromatase inhibitor plus lapatinib/trastuzumab is superior to an aromatase inhibitor plus either trastuzumab or lapatinib in regard to PFS (11.0 vs 5.6 months, respectively).

Two recently published trials, monarcHER[47] and SOLTI-1303 PATRICIA,[48] have studied the use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with HER2 antibodies. Work by Goel and colleagues[49] has shown that CDK4/6 inhibitors can overcome HER2 tumor cell resistance to anti-HER2 agents in preclinical models. MonarchHER, a phase 2 trial,[47] randomly assigned patients to receive fulvestrant, abemaciclib (Verzenio, Lilly), and trastuzumab (arm A); abemaciclib and trastuzumab (arm B); or standard chemotherapy plus trastuzumab (arm C) in the third-line setting. According to prespecified statistical significance, a significant improvement in median PFS was observed with fulvestrant plus abemaciclib/trastuzumab: 8.3 months in arm A vs 5.7 months in arm C (HR, 0.67; 95% CI, 0.45-1.00; *P*=.051). Data on OS were still immature at the time of analysis. ORRs with the triplet regimen were more than double those in arms B and C (33%, 14%, and 14%, respectively; *P*=.0042). Although the risk for diarrhea, nausea, and vomiting was higher in arm A, the rates of treatment discontinuation and quality of life were similar in the 3 groups. The SOLTI-1303 PATRICIA trial[48] also evaluated the role of a CDK4/6 inhibitor plus trastuzumab in HER2-positive disease. This 3-cohort trial, with a Simon 2-stage design, evaluated trastuzumab plus palbociclib (Ibrance, Pfizer) in cohort A (patients with ER-negative disease), cohort B1 (patients with ER-positive disease not treated with letrozole), and cohort B2 (patients with ER-positive disease treated with letrozole). PFS and ORRs were superior in cohort B2, with acceptable adverse event profiles. An interesting subgroup analysis by intrinsic tumor subtype showed that luminal-subtype tumors derived the greatest benefit from palbociclib plus trastuzumab. On the basis of these findings, the PATRICIA study (NCT02448420) is now testing whether palbociclib, trastuzumab, and endocrine therapy is superior to physician treatment of choice for luminal tumors.

The PATINA trial[50] is also evaluating CDK4/6 inhibitors in this scenario. This open-label phase 3 study is evaluating HER2 blockade plus endocrine therapy with or without palbociclib after an initial induction phase of chemotherapy plus anti-HER2 treatment.

HER2-Positive Breast Cancer and Immune Checkpoint Inhibition

Immune checkpoint–blocking agents that target programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1), in combination with chemotherapy, have shown clinical efficacy in patients with PD-L1–positive triple-negative breast cancer.[51] Preclinical data have shown that HER2-positive tumors are highly immunogenic, and trastuzumab boosts the immune response against the tumor.[52] Consistent data demonstrate not only a high incidence of tumor-infiltrating lymphocytes but also a high level of expression of PD-L1 in HER2-positive tumors, and both are correlated with better outcomes.[53,54] However, data on the combination of anti–PD-L1 agents and HER2 blockade are still sparse. The PANACEA trial, which investigated the use of trastuzumab plus pembrolizumab (Keytruda, Merck) in trastuzumab-resistant HER2-positive MBC,[55] found a tolerable safety profile but a modest ORR of 15% in patients with PD-L1–positive tumors. Similarly, the phase 2 KATE2 trial[56] demonstrated that the combination of T-DM1 with atezolizumab (Tecentriq, Genentech) as second-line treatment is safe, but clinical benefit was observed only in patients with PD-L1–expressing tumors. After a median follow-up of 19.5 months, the intention-to-treat PFS was not significant (8.2 months for atezolizumab vs 6.8 months for placebo; HR, 0.82; 95% CI, 0.55-1.23; *P*=.33). An exploratory analysis of PD-L1–positive patients showed increased PFS in the atezolizumab arm (8.5 vs 4.1 months; HR, 0.60; 95% CI, 0.32-1.11).

Overall, data from the PANACEA and KATE2 trials show that immunotherapy in combination with anti-HER2 therapy warrants further evaluation, and multiple trials are ongoing, including NRG-BR004 (NCT03199885), IMpassion050 (NCT03726879), and TOPAZ (NCT04512261).

Biomarkers Predictive of Response

HER2 Levels

HER2 levels and tumor heterogeneity are emerging as sensitive biomarkers in either early or advanced disease. Tumors with low HER2 levels are defined as those with an IHC score of 2 and amplification on FISH, and tumors with high HER2 levels are defined as those with an IHC score of 3. In the CLEOPATRA trial,[57] patients with low levels of HER2 expression had worse PFS than did the patients with high levels of expression by IHC (HR, 0.83; 95% CI, 0.69-1.00; *P*=.0502); however, this finding was not predictive of a better response to trastuzumab/pertuzumab than to single blockade and is consistent with the findings of MARIANNE[58] and TH3RESA.[59] Although the prognostic value of HER2 expression levels was substantial, HER2 levels were not predictive of benefit from T-DM1 treatment.[60]

HER2 Heterogeneity

Intratumoral heterogeneity of HER2 expression, defined as the presence of varying degrees of HER2 overexpression in different areas within the same tumor, has been reported in 16% to 36% of patients with HER2-positive breast cancer.[61] Metzger and colleagues[62] classified as heterogeneous tumors that had at least 1 area of HER2 negativity or HER2 positivity on a FISH test in fewer than 50% of cells; in addition, such tumors demonstrated the absence of a pathologic complete response to HER2-guided therapy in the early setting. The updated analysis of the KRISTINE trial[63] showed similar findings; the response of patients with heterogeneous tumors to T-DM1 plus pertuzumab was worse than their response to standard chemotherapy. HER2 heterogeneity also has an effect in the metastatic setting, and low-level or equivocal *HER2* amplification is significantly correlated with a poor response to trastuzumab and T-DM1.[64]

A post hoc analysis of the MARIANNE trial[58] evaluated the effect of tumor heterogeneity. Although heterogeneous tumors had a worse response to T-DM1 numerically, the difference was not statistically significant owing to the small sample size.

A phase 1 trial by Modi and colleagues[65] showed promising clinical antitumor activity of trastuzumab deruxtecan in patients considered to be HER2-low or -heterogeneous, which was probably due to the high drug-to-antibody ratio of this agent, allowing high levels of payload to be delivered into the HER2-expressing cancer cells.

PIK3CA Mutation

PIK3CA mutation is observed in 20% to 30% of patients with HER2-positive MBC.[66] Although trials have consistently demonstrated that *PIK3CA* mutation is correlated with anti-HER2 drug resistance and worse survival, no predictive value has been observed.[57-60] The phase 3 EPIK-B2 trial (NCT04208178) is randomly assigning patients to receive either alpelisib (Piqray, Novartis) or placebo in combination with dual anti-HER2 therapy as maintenance treatment.[67]

Future Directions

In recent years, a better understanding of tumor biology and the development of new drugs have dramatically changed the natural history of HER2-positive MBC and consequently improved patients' outcomes. However, we still need to identify reliable biomarkers and the most effective treatment sequence (see the Figure for a comprehensive approach to the treatment of HER2-positive MBC). Intratumoral heterogeneity is a growing field of research in HER2-positive disease, and the findings may be briefly incorporated into clinical practice in the adjuvant setting; however, more studies of patients with metastatic disease are needed. Also, data on new combinations of anti-HER2 drugs with immune checkpoint inhibitors and/or CDK4/6 inhibitors are ongoing, and new treatment options may be available in the near future.

Newer agents, such as margetuximab and pyrotinib, have produced encouraging results. Margetuximab is an investigational anti-HER2 antibody that is optimized for the Fc domain and has increased immunomodulatory activity. Compared with trastuzumab, margetuximab binds more intensively to Fc-gamma receptor IIIA (CD16A), which is expressed on natural killer cells and macrophages, consequently enhancing immune-mediated cytotoxicity.[68] SOPHIA[69] is an ongoing phase 3 trial that is enrolling patients to receive margetuximab plus chemotherapy or trastuzumab plus chemotherapy after 2 previous lines of anti-HER2 therapy. A modest increase in PFS (median PFS, 5.8 vs 4.9 months; HR, 0.76; 95% CI, 0.59-0.98; *P*=.033) and no benefit in OS were noted; however, an exploratory analysis found that margetuximab showed a trend toward improved OS vs trastuzumab exclusively in patients with the CD16A-F allele (23.7 vs 19.4 months; *P*=.087), whereas no gain was observed in patients with the CD16A-158VV allele.

Pyrotinib is a new pan-HER2 TKI that potently inhibits EGFR/HER1, HER2, and HER4 irreversibly. A phase 2 study randomly assigned patients to receive pyrotinib vs lapatinib in combination with capecitabine.[70] The ORR (78.5% vs 57.1%) and the PFS (18.1 vs 7.0 months; HR, 0.36; 95% CI, 0.23-0.58; *P*<.001) were impressively better in the pyrotinib group than in the lapatinib group, but the incidences of hand-foot syndrome and diarrhea were significantly higher.

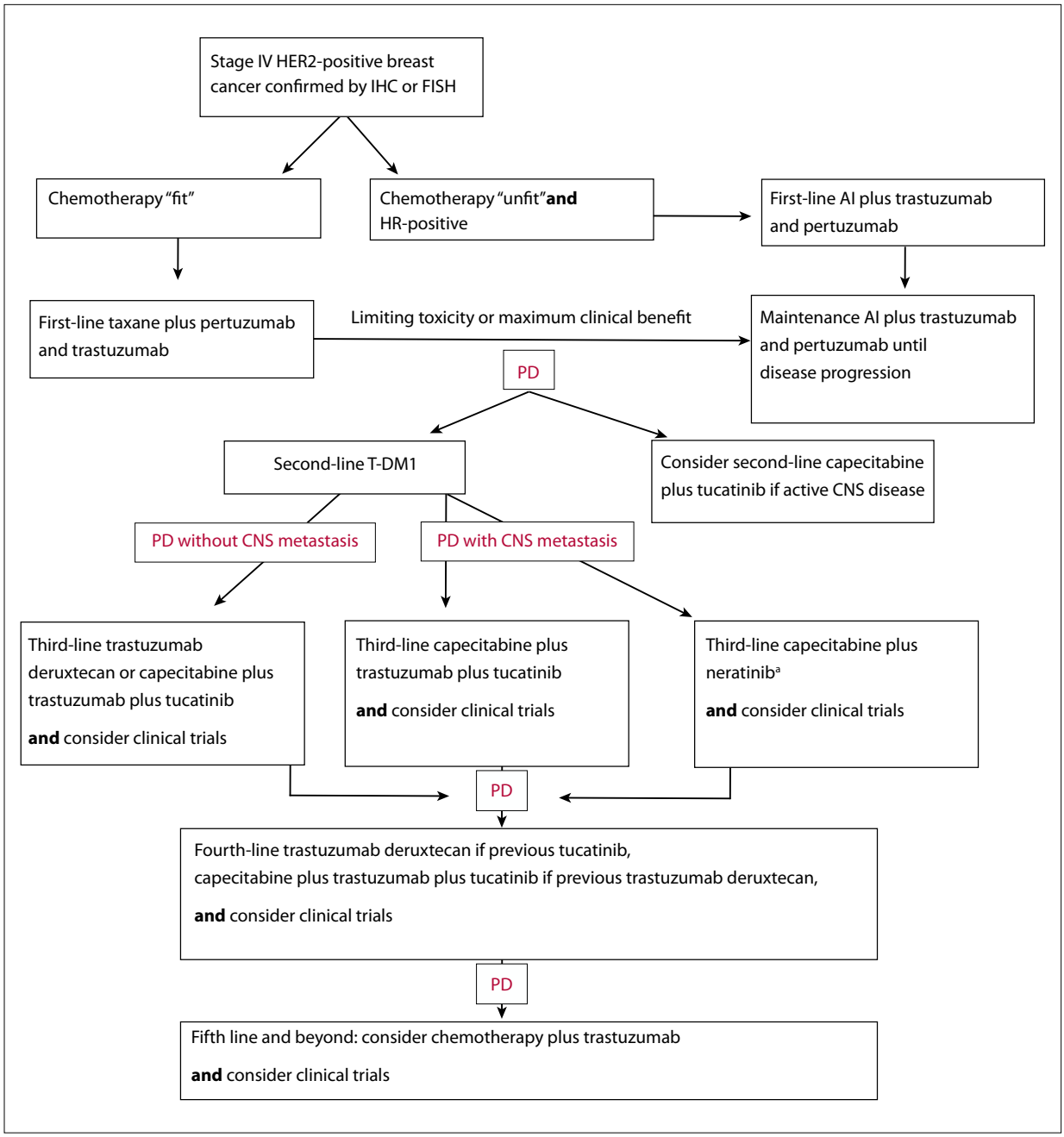

Figure. Comprehensive approach to the treatment of stage IV HER2-positive breast cancer.

AI, aromatase inhibitor; CNS, central nervous system; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; PD, progression of disease; T-DM1, trastuzumab emtansine.

[a]Tucatinib regimen is preferred if available given overall survival benefit and less toxicity.

Conclusions

We have achieved significant progress in the treatment of HER2-positive MBC. Overexpression of this membrane protein, initially classified as a biomarker for a poor prognosis, has now become a targetable molecular alteration, drugs for which have greatly improved patient quality of life and long-term survival.[71] The emergence of increasingly effective drugs, such as tucatinib and trastuzumab deruxtecan, makes treatment sequencing

challenging, and more data identifying helpful biomarkers are essential to guide a determination of the best treatment option for each patient.

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