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Review

Solving the Puzzle of Treatment Resistance in Patients with HER2-Positive Metastatic Breast Cancer – New Approaches to HER Target Family Network

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Abstract

In the last twenty years, there has been remarkable progress in the development of therapies for human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC), and now, systemic therapy is a key component of the metastatic BC management. Modern therapies for patients with HER2-positive metastatic BC include targeted anti-HER2 monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), tyrosine kinase inhibitors (TKIs), and chemotherapy (CHT) (e.g., capecitabine). Consequently, various HER2-targeted agents, such as trastuzumab and pertuzumab (mAbs), trastuzumab emtansine (T-DM1) (an ADC), as well as lapatinib (a TKI) have been recommended as key components of the standard of care regimens for patients suffering from HER2-positive BC.

This mini-review outlines possible mechanisms of resistance to common anti-HER2 treatments. In addition, this paper highlights novel HER2-targeted therapeutic strategies for the systemic treatment of patients with HER2-positive metastatic BC, including margetuximab (a novel mAb), trastuzumab deruxtecan (a high potency ADCs), and tucatinib (a selective TKI), based on the results of recent clinical trials. Furthermore, this article briefly comments on the phosphatidylinositol-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) inhibitors and anti-HER3 approaches, in women with metastatic BC.

This overview also addresses some possible advantages of immune checkpoint inhibitors and cyclin-dependent kinase (CDK) 4/6 inhibitors used in combination with anti-HER2 therapies for patients with HER2-positive metastatic BC, as well as some management issues, aiming at bridging the gap between the guidelines and the challenges of daily practice in individual women with HER2-positive metastatic BC.

Keywords: Antibody-drug conjugates (ADCs), breast cancer (BC), human epidermal growth factor receptor 2 (HER2), metastatic BC, monoclonal antibodies (mAbs), treatment resistance, tyrosine kinase inhibitors (TKIs)

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During the past two decades, there has been remarkable progress in the development of targeted therapies for human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC), and now, systemic therapy is a key component of the metastatic BC management.[1] However, in spite of unquestionable clinical benefits, which have been accomplished with HER2-targeted therapies, HER2-positive metastatic BC still remains an incurable disease. This unfortunate situation has been further aggravated by the frequent development of resistance to HER2-directed medications. To address this unmet medical need, an explanation of the complex resistance mechanisms is a necessary step for the development of innovative therapeutic solutions to improve the patient outcomes.[1] However, an accurate interpretation of mechanisms of resistance is very difficult, because of the tumor heterogeneity and, interrelated compensatory signal-

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ing HER pathways. Moreover, multiple mechanisms of resistance may coexist in the same cell.[1]

Currently, the main therapies indicated for patients with HER2-positive metastatic BC include targeted anti-HER2 monoclonal antibodies (mAbs) (e.g., trastuzumab and pertuzumab), antibody-drug conjugates (ADCs) (e.g., trastuzumab emtansine (T-DM1)), tyrosine kinase inhibitors (TKIs) (e.g., lapatinib), and chemotherapy (CHT) (e.g., taxanes or capecitabine).[2] In addition to these therapies, some promising options involve the innovative anti-HER2 mAbs (e.g., margetuximab),[3] high potency ADCs (e.g., trastuzumab deruxtecan),[4] and selective TKIs (e.g., tucatinib).[5] There is no question that overcoming resistance to HER2-targeted therapies is very challenging. However, exploring the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signalization pathway and HER3 activation sheds some light on solving this problem in women with HER2-positive metastatic BC.[6, 7]

This mini-review outlines possible mechanisms of resistance to common anti-HER2 treatments. In addition, this paper highlights novel HER2-targeted therapeutic strategies for the systemic treatment of patients with HER2-positive metastatic BC, including margetuximab, trastuzumab deruxtecan, and tucatinib, based on the results of recent clinical trials. Furthermore, this article briefly comments on PI3K/AKT/mTOR inhibitors and anti-HER3 approaches, in women with metastatic BC. This overview also addresses some possible advantages of selected immune checkpoint inhibitors and cyclin-dependent kinase (CDK) 4/6 inhibitors, used in combination with anti-HER2 therapies for patients with HER2-positive metastatic BC as well as some management issues, aiming at bridging the gap between the guidelines and the challenges of daily practice in individual women with HER2-positive metastatic BC.

Mechanisms of Resistance to Anti-HER2 Treatments in Metastatic BC – Focus on PI3K/AKT Signaling Pathway

HER2 is a transmembrane receptor tyrosine kinase (RTK) that belongs to the HER family, together with other receptors, including HER1, HER3, and HER4, as well as over ten ligands.[1] It should be noted that HER2 (in contrast to the other HER receptors) does not have its particular ligand, and HER3 does not exert intrinsic tyrosine kinase (TK) activity.[8]

HER receptors can create homodimers or heterodimers, which undergo transphosphorylation of the TK domains, and then stimulate downstream signaling by the phosphatidylinositol-3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and the RAS/mitogen-activated protein kinase (MAPK) pathways.[6, 8] In fact, the PI3K/AKT signaling pathway has a profound impact on the cell growth, proliferation, migration and apoptosis. Induction of the PI3K/AKT pathway enables the expression of genes responsible for malignant cell proliferation, growth, angiogenesis, local invasion, and metastatic spread.[6, 8]

Moreover, it needs to be kept in mind that HER2 is the most prominent, while HER2/HER3 heterodimer has probably the highest oncogenic propensity.[7, 8] Consequently, if the HER2 gene amplification is present or the HER2 protein is overexpressed (as it happens in about 20% of BCs), the downstream pathways are mediated via aberrant signal transduction (e.g., by the hyperactivation of PI3K/AKT and RAS/MAPK signaling pathways).[6, 8] The PI3K/AKT activation can also be related to endocrine resistance and worse prognosis in certain subgroups of women with ER-positive metastatic BC. At this point, resistance (both primary and acquired) to HER2-directed medications can develop during the treatment process, contributing to BC progression and negative clinical outcomes. It should be highlighted that the mechanisms of resistance to anti-HER2 therapies usually involve an abnormal activation of the HER2 or ER escape pathways via redundant communication networks. Consequently, breast tumors co-expressing HER2 and ER are less sensitive to endocrine therapy (ET) than the ER-positive/HER2-negative BCs. Since ER may serve as an escape pathway to the HER2 inhibition, concomitant blocking of ER (with ET) together with HER2 (with anti-HER2 blockade) can improve patient outcomes (Fig. 1).[1, 7, 8]

In addition, it should be noted that changes in downstream signaling pathways, via hyperactivation of the PI3K/AKT/mTOR pathway, related to decreased levels of tumor suppressor genes (e.g., phosphatase and tensin homolog (PTEN)) or due to activating mutations in PIK3CA can also contribute to the therapeutic resistance).[6, 8] At this point, it should be noted that the mTOR pathway, which integrates both intracellular and extracellular signals and serves as a central regulation of cell metabolism, development, proliferation and survival, can also play a role of the novel therapeutic target.[8]

A Spotlight on HER3-Mediated Signaling and its Impact on Therapeutic Resistance

It should be emphasized that HER3 as a key heterodimeric component (for other HER particles), is capable of the regulation of resistance to anti-HER2 and ET treatments (e.g., via the activation of PI3K/AKT signaling pathway).[7, 8] On the other hand, however, activating mutations in HER3 have revealed some beneficial role of HER3 as an innovative

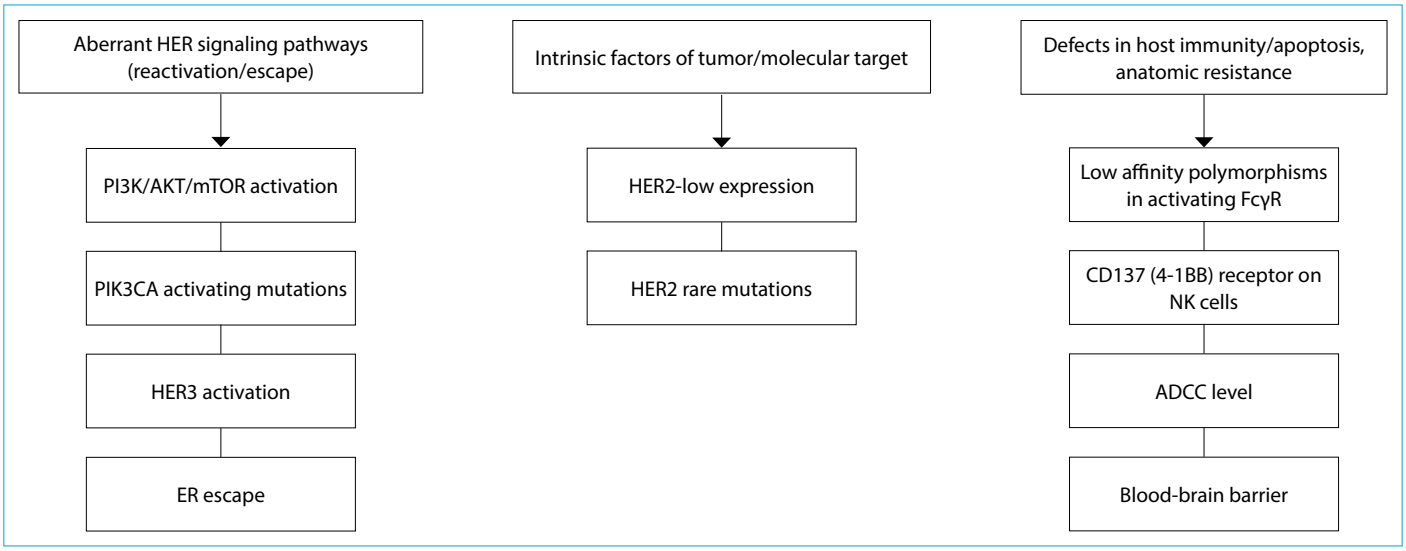

Figure 1. The main mechanisms of resistance to anti-HER2 therapies in patients with HER2-positive metastatic BC.[1, 7, 8]

ADCC: antibody-dependent cellular cytotoxicity; BC: breast cancer; CD137 (4-1BB): the costimulatory receptor on natural killer cells; ER: estrogen receptor; FcγR: Fcγ receptor; HER2: human epidermal growth factor receptor 2; HER3: human epidermal growth factor receptor 3; NK: natural killer; PI3K/AKT/mTOR: phosphatidylinositol-3 kinase/protein kinase B/mammalian target of rapamycin signaling pathway.

treatment target, where small molecules, such as TKIs (e.g., neratinib) can be applied, by binding to the TK extracellular domain.[7, 8]

It should be highlighted that HER3 plays a key role in HER signalization network and HER2-directed treatment resistance.[7] Noticeably, applying novel TKIs in order to target other HER family members can contribute to feedback up-regulation of HER3. This, in turn, may enhance the direct targeting of HER3, creating a possible therapeutic option.[7] Although some anti-HER3 mono- and bispecific antibodies and small molecule inhibitors have revealed efficacy, the HER3-targeted treatment is still not approved for the clinical use.[7] Nevertheless, it is conceivable that concurrent suppression of HER3 and other HER family members can be useful for achieving beneficial therapeutic effects in women with HER2-positive BC.[7]

Promising Therapeutic Strategies to Combat Resistance and Improve Prognosis in Patients With HER2-Positive Metastatic BC

Resistance is a well-known cause of treatment failure, which reduces the efficacy of many HER2-targeted agents (e.g., mAbs and TKIs) in patients with HER2-positive BC.

Since the resistance to anti-HER2 agents can often be caused by HER2 pathway reactivation/redundancy and possible use of escape pathways (via ER) (Fig. 1),[8] recent attempts to overcome these obstacles are focused on novel treatments that block different components of the HER family signaling network.[8]

In addition, due to some defects in host immunity and specific anatomic resistance conditions (e.g., in the central nervous system (CNS)), innovative treatments are designed to interfere with some host immune factors or anatomical conditions (e.g., CNS) (Fig. 1).[8]

In particular, such innovative strategies to combat resistance to standard HER2-targeted therapies include the following (Table 1):

(a) Fc domain-engineered anti-HER2 monoclonal antibody (e.g., margetuximab) – designed to reduce resistance secondary to low-affinity activating Fcγ receptors (FcγR),[3]

(b) ADCs (e.g., trastuzumab deruxtecan and trastuzumab duocarmazine) – aimed at overcoming resistance caused by PIK3CA mutation,[4, 9, 10–12]

(c) selective TKIs (e.g., tucatinib) – geared towards overcoming anatomic resistance associated with the blood-brain barrier (that is especially helpful in the case of brain metastases due to HER2-overexpressing BC).[5]

Noticeably, margetuximab binds with increased affinity to both lower- and higher-affinity forms of FcγR. In this way, margetuximab elicits potent antibody-dependent cellular cytotoxicity (ADCC) reactions, even in patients with low-affinity activating FcγRs.[3] In addition to this advantage, margetuximab has been well tolerated (e.g., without the increase in cardiotoxicity events).[3] In the SOPHIA trial (phase 3, NCT02492711), margetuximab has revealed its benefits, when compared to trastuzumab (in combination with CHT) among women with HER2-positive metastatic BC (after prior anti-HER2 therapy) (Table 1).[3]

It is worth keeping in mind that antibody-dependent cel-

Table 1. Recent clinical trials addressing resistance to anti-HER2 therapies in patients with HER2-positive metastatic breast cancer

Clinical trial, phase, identifier	Therapeutic agent/class	Trial intervention	Practical implications/patient outcomes	Author [ref.]
SOPHIA Phase 3 NCT02492711	Margetuximab Anti-HER2 mAB (Fc-engineered region)	Margetuximab + CHT vs. trastuzumab + CHT	Margetuximab + CHT, in pts with HER2-positive mBC (after anti-HER2 therapy, e.g. pertuzumab), improved PFS compared to trastuzumab + CHT; PFS benefits were stronger in low-affinity CD16A-158F allele carriers subgroup of pts	Rugo et al. 2019[3]
DESTINY-Breast01 Phase 2 NCT03248492	Trastuzumab deruxtecan (DS-8201) Anti-HER2 ADC, (Topoisomerase, I inhibitor)	Trastuzumab deruxtecan (open-label, single-group)	Ttrastuzumab deruxtecan revealed durable antitumor activity in pretreated (with T-DM1) pts with HER2-positive mBC; in the trastuzumab deruxtecan arm: ORR = 60.3%; median PFS = 16.4 ms; interstitial lung disease is a serious AE that requires vigilant monitoring/therapy	Modi et al. 2020[4]
Phase 1 NCT02277717	Trastuzumab duocarmazine (SYD985) Anti-HER2 ADC (Duocarmycin derivative – an alkylating agent)	Trastuzumab duocarmazine (dose-escalation/dose-expansion)	Trastuzumab duocarmazine has shown clinical activity in pretreated pts with HER2-positive mBC (HER2-positive, T-DM1-resistant, HER2-low BC), with manageable safety; ORR in HER2-positive BC = 33%; ORR in HER2-low, HR-positive BC = 27%; ORR in HER2-low, HR-negative BC = 40%	Banerji et al. 2019[11]
HER2CLIMB Phase 3 NCT02614794	Tucatinib A selective HER2 TKI	Tucatinib vs. placebo (in both arms combination: capecitabine/trastuzumab [C/T]	In pretreated pts with HER2-positive mBC (including those with CNS metastases) adding tucatinib to a combination of C/T resulted in longer PFS (7,6 vs. 5,4 ms) and OS (21,9 vs. 17,4 ms) compared to the placebo arm; tucatinib exerts a stronger activity (than other TKIs) for CNS metastases and has a lower rate of AEs (e.g., skin reactions, diarrhea)	Murthy et al. 2019[5]
NALA Phase 3 NCT01808573	Neratinib An irreversible pan HER2 TKI	Neratinib/capecitabine [N/C] arm vs. Lapatinib/capecitabine [L/C] arm	In pretreated pts with HER2-positive mBC, in the N/C vs. L/C arm: PFS rates = 28.8% vs. 14.8%; OS rates = 72.5% vs.66.7%; ORR = 32.8% vs 26.7%; CBR = 44.5% vs. 35.6% activity for CNS metastases	Saura et al. 2019[15]
Phase 2 NCT003080805	Pyrotinib An irreversible pan HER2 TKI	Pyrotinib/capecitabine [P/C] arm vs. Lapatinib/capecitabine [L/C] arm	Pyrotinib or lapatinib (with capecitabine) in pts with HER2-positive mBC (post treatment with in the arm: anthracyclines/taxanes/trastuzumab); P/C: ORR = 78.5%; median PFS = 18.1 ms, L/C: ORR = 57.1%; median PFS = 7.0 ms	Ma et al. 2019[20]
NOV120101-203 Phase 2 NCT02418689	Poziotinib An irreversible pan HER2 TKI	Poziotinib as monotherapy (single-arm trial)	PFS = 4 ms; DCR = 75% in pretreated pts with HER2-positive mBC	Park et al. 2018[21]

Table 1. CONT.

Clinical trial, phase, identifier	Therapeutic agent/class	Trial intervention	Practical implications/patient outcomes	Author [ref.]
BOLERO-1 Phase 3 NCT00876395	Everolimus mTOR inhibitor	Everolimus with trastuzumab + paclitaxel	Everolimus in combination with trastuzumab + paclitaxel as first-line treatment for pts with HER2-positive mBC (PFS was 7,2 ms longer with adding everolimus in HR-negative, HER2-positive mBC)	Hurvitz et al. 2015[17]
BOLERO-3 Phase 3 NCT01007942	Everolimus mTOR inhibitor	Everolimus with trastuzumab + vinorelbine vs. placebo with trastuzumab + vinorelbine	Everolimus in combination with trastuzumab + vinorelbine in pts with HER2-positive mBC (pretreated with a taxanes) has shown benefits: median PFS = 7.0 ms in the combination arm vs. 5.78 ms in the placebo arm	Andre et al. 2014[18]
MonarcHER Phase 2 (ongoing) NCT02675231	Abemaciclib CDK4/6 inhibitor	Abemaciclib + trastuzumab with/without fulvestrant vs. trastuzumab + CHT	Combination of abemaciclib + trastuzumab and fulvestrant in pts with pretreated HR-positive, HER2-positive mBC, has shown benefits: median PFS = 8.3 ms, vs. 5.7 ms for trastuzumab + CHT; response rate with the combination = 33%	Tolaney et al. 2019[29]
PATINA Phase 3 (ongoing) NCT02947685	Palbociclib CDK4/6 inhibitor	Palbociclib + anti-HER2 therapy + ET vs. anti-HER2 therapy + ET	Palbociclib added to trastuzumab, pertuzumab and an AI vs. anti-HER2 therapy + ET, after induction treatment for HR-positive/HER2-positive mBC; evaluation of PFS with using the combination of palbociclib with anti-HER2 therapy + ET vs. anti-HER2 therapy + ET alone; (pending OS, tumor control, safety, and QoL)	Loibl et al. 2018[30]
PANACEA Phase 1b-2 NCT02129556	Pembrolizumab PD-L1 inhibitor	Pembrolizumab + trastuzumab (single-arm trial)	Pembrolizumab + trastuzumab in trastuzumab-resistant, HER2-positive mBC; in PD-L1-positive subgroup of pts, the combination revealed durable clinical benefits/acceptable safety; ORR = 15%	Loi et al. 2019[23]
KATE2 Phase 2 NCT02924883	Atezolizumab PD-L1 inhibitor	Atezolizumab + T-DM1 vs. placebo + T-DM1	Atezolizumab added to T-DM1 in pts with HER2-positive mBC did not significantly increase PFS compared to T-DM1 + placebo in the ITT group; however, PFS was longer in PD-L1-positive subgroup of pts	Emens et al. 2019[24]

ADC, antibody drug conjugate; AEs, adverse events; AI, aromatase inhibitor; BC, breast cancer; CDK, cyclin dependent kinase; CHT, chemotherapy; CNS, central nervous system; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intent to treat; m, metastatic; mAb, monoclonal antibody; ms, months; mTOR, mechanistic target of rapamycin; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PI3K, the phosphoinositide 3-kinase; QoL, quality of life; ref., reference; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; vs., versus.

lular cytotoxicity (ADCC) can also be increased via activation of the costimulatory receptor CD137 (4-1BB), located on natural killer (NK) cells, by using agonist antibodies. CD137 agonists augment cytotoxic T-cell responses that result in anti-tumor activity. For instance, utomilumab (PF-05082566) is a fully humanized IgG2 agonist monoclonal antibody targeting 4-1BB.[13] Stimulation of trastuzumab-activated human NK cells with agonistic mAb specific for CD137 has been lethal for BC cells (even if such BC cells were previously resistant to trastuzumab).[13] In fact, the dual antibody approach (which combines a tumor-targeting antibody with an antibody that stimulates the host primary immunity) can augment the treatment results in patients with HER2-positive BC.[13] A clinical trial of agonist CD137 antibody utomilumab in combination with trastuzumab or T-DM1 is currently underway (NCT03364348).[8]

It should be recognized that novel ADCs, such as trastuzumab deruxtecan (DS8201)[4] and trastuzumab duocarmazine (SYD985),[11] as targeted agents, combining the selectivity of monoclonal antibodies with the cytotoxicity of chemotherapeutics, offer promising strategies for many women with HER2-positive metastatic BC, who developed resistance to prior lines of treatment (e.g., trastuzumab emtansine (T-DM1)).[9] Trastuzumab deruxtecan (DS8201) is an ADC which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the topoisomerase I inhibitor, deruxtecan (a cytotoxic payload).[4] The approval of Trastuzumab deruxtecan reflects the innovative treatment strategy for patients who have progressed on prior lines of anti-HER2 therapy (e.g., trastuzumab, pertuzumab, T-DM1, and other targeted agents), and is based on results from the DESTINY-Breast01 trial (phase 2, NCT03248492) (Table 1).[4]

Trastuzumab duocarmazine (SYD985) consists of trastuzumab, a "cleavable" linker, and duocarmycin payload (an alkylating agent), in the form of inactive prodrug.[11] Upon the release, cytotoxic payload irreversibly binds to the DNA, causing cell death not only in dividing and nondividing cells in the tumor microenvironment, but also in neighboring tumor cells (via the "bystander effect").[11] SYD985 has revealed clinical activity and acceptable safety profile in pretreated women with metastatic BC (HER2-positive and T-DM1-resistant), as well as in those with HER2-low expression BC.[11] Further exploration of SYD985 for HER2-positive and HER2-low BC are in process (Table 1).[11]

A clinically important type of resistance is relevant to the brain microenvironment, in which there is a vascular structure known as blood-brain barrier (BBB) that can facilitate a formation of the CNS metastatic niche.[14] Unfortunately, HER2-positive BC spreads to the CNS, in approximately 50% of patients, despite the use of standard therapy with anti-HER2 monoclonal antibodies (e.g., trastuzumab and pertuzumab).[14] In fact, a large size of monoclonal antibodies is an obstacle to their penetration across the BBB.[14] In response to this challenge, some novel, capable of crossing the BBB small molecules HER2 TKIs have been developed for treatment of HER2-positive brain metastasis. After some initial modest effects that have been shown with the use of the combination of TKI, lapatinib with capecitabine, more beneficial effects have been revealed with the use of another TKI, neratinib, combined with capecitabine (NALA trial, phase 3, NCT01808573) (Table 1).[15] Furthermore, a highly HER2-selective TKI, tucatinib, in combination with capecitabine and trastuzumab, based on the HER2CLIMB trial (phase 3, CT02614794), has shown relatively good efficacy for CNS metastases and an acceptable tolerability profile (e.g., due to its selectivity for HER2, there have been fewer EGFR-related toxic effects, like diarrhea and skin rash, which are common with other anti-HER TKIs) (Table 1).[5]

Deciphering The PI3K/AKT/mTOR Signaling Code and Considering the use of mTOR Pathway Inhibitors

The PI3K/AKT/mTOR intracellular signaling plays a key role in governing the cell growth, proliferation, migration and apoptosis. However, this pathway is often dysregulated in patients with BC, and in consequence, resistance (both primary and secondary) to HER2-targeted agents and endocrine therapies (ET) may develop.[16] For instance, activation of the PI3K/AKT/mTOR pathway has been linked to endocrine resistance and worse prognosis in certain subgroups of patients with BC. In addition, PIK3CA activating mutations are frequently present in BC and multiple efforts have been carried out to target these abnormalities.[16] For instance, based on the data from some recent phase 3 studies, everolimus, which is a blocking agent of the mTOR pathway, has revealed beneficial effects in women with trastuzumab-resistant HER2-positive metastatic BC.[16]

In particular, BOLERO-1 (phase 3, NCT00876395) trial has evaluated the combination of everolimus, trastuzumab, and paclitaxel, as first-line treatment,[17] and BOLERO-3 (phase 3, NCT01007942) trial has assessed whether the addition of everolimus to trastuzumab can restore sensitivity to trastuzumab (Table 1).[18] In the BOLERO-1, PFS was not significantly different between arms; however, it was prolonged with the addition of everolimus, in a group of women with HR-negative, HER2-positive advanced or metastatic BC.[17] According to the BOLERO-3 an addition of everolimus to trastuzumab plus vinorelbine significantly prolongs PFS in patients with trastuzumab-resistant, taxane-pretreated women with HER2-positive, advanced or metastatic BC.[18] In essence, the findings of BOLERO-1 and BOLERO-3 trials have shown that patients with PIK3CA

mutation, PTEN deletion, or PI3K pathway activation of HER2-positive BC (who had progressed on previous therapies) can benefit from everolimus, in terms of longer PFS.[17, 18] However, further investigation of mTOR inhibitors and their combinations with trastuzumab and CHT, focused on the evaluation of efficacy and safety in the metastatic BC setting are warranted.

A Possible Role of New Generation of Tyrosine Kinase Inhibitors (TKIs) in Overcoming Resistance to HER2-Targeted Agents

Pyrotinib is an irreversible pan-HER kinase TKI.[19] Pyrotinib binds to ATP-binding sites in the intracellular kinase region of HER1, HER2, and HER4. This blocks both the formation of HER family homodimer and the activation of downstream signaling pathways. This, in turn, apprehends the tumor cell growth.[19] Pyrotinib has been reported to contribute to the remarkable progression-free survival (PFS) (up to 18.1 months).[20] Recently, a phase 2 clinical study has compared combination of pyrotinib with capecitabine and lapatinib with capecitabine, for the treatment of the patients with advanced HER2-positive BC (who were previously treated or not treated with trastuzumab).[20] It has been reported that the ORR of patients in the pyrotinib arm was higher than that in the lapatinib arm, and the median PFS in the pyrotinib arm was significantly longer, (compared to the lapatinib arm (Table 1).[20] Poziotinib is a potent irreversible pan-HER kinase TKI that has been investigated in a single-arm NOV120101-203 (phase 2, NCT02418689) trial, assessing its efficacy and safety, among pretreated women with HER2-positive metastatic BC. According to findings of this study, median PFS was 4 months (Table 1).[21]

Advantages of Immune Checkpoint Inhibitors for Patients with HER2-Positive Metastatic BC

Programmed death ligand 1 (PD-L1) is an immunoglobulin superfamily haplotype type I transmembrane glycoprotein (related to apoptosis) that is widely expressed on the surface of lymphocytes, monocytes, macrophages, and many other cells.[22] Similarly, programmed cell death protein-1 (PD-1), which is an inhibitory immune checkpoint that limits T-cell effector functions within tissues, is expressed on the surfaces of immune effector cells (such as T-cells, B cells, natural killer (NK) cells, dendritic cells (DCs), and tumor infiltrating lymphocytes (TILs)).[22] Recently, some novel immunomodulatory agents, including immune checkpoints inhibitors, have shown promising effects in subgroups of women with metastatic BC.[22] Since ADCC represents a mechanism of action of mAbs (e.g., trastuzumab), the combination of mAb and immune checkpoint inhibitor can augment therapeutic activity and combat acquired resistance among women with HER-2 positive metastatic BC (pretreated with CHT and anti-HER2 mAbs).[22]

HER2-positive BCs often contain large amounts of TILs and anti-HER2 mAbs act synergistically with PD-L1 inhibitors.[22] In particular, anti-PD-L1 antibodies (that inhibit PD-L1 binding to PD-1) are capable of restoring antitumor immunity. It should be noted that the resistance to trastuzumab in patients with HER2-positive BC have been mediated, to a large degree, by the immune reactions.[22] Based on the findings of PANACEA trial (phase 1b-2 NCT02129556), an addition of a PD-L1 inhibitor, pembrolizumab (an anti-PD-L1 antibody), to trastuzumab (in trastuzumab-resistant, HER2-positive BC) has demonstrated clinical benefits and safety in the PD-L1-positive population of patients with HER2-positive metastatic BC (Table 1).[23]

Similarly, results from a phase 2 KATE2 trial (phase 2, NCT02924883) evaluating the efficacy and safety of T-DM1 in combination with another PD-L1 inhibitor, atezolizumab, or placebo, in previously treated women with HER2-positive advanced BC, have revealed that although adding atezolizumab to T-DM1 had not demonstrated a large PFS benefit in the intent to treat (ITT) population (8.2 vs. 6.8 months), a more favorable PFS has been noted in the cases of PD-L1 positive and stromal TIL subgroups of patients.[24] Moreover, according to the KATE2 trial findings, a therapy with atezolizumab and T-DM1 in PD-L1-positive women has led to a possible OS benefit. However, due to the small sample and short follow-up period, further trials are needed to confirm these results.[24] At present, ongoing studies investigate a combination of immunotherapy and HER2-targeted therapy, focusing on the specific biomarkers (e.g., PD-L1) aiming at selection of the most appropriate patient candidates for such combination treatments.[22, 24]

Impact of Cyclin-Dependent Kinase (CDK)4/6 Inhibitors on the Therapeutic Strategies in Patients with HER2-Positive Metastatic BC

Cyclin-dependent kinase (CDK) 4/6 inhibitors are a new class of agents, which induce cell cycle arrest and can slow down malignant growth or prevent tumor progression.[25] In particular, the CDK 4/6 inhibitors block an activity of the cyclin D-CDK 4/6 holoenzyme, and stop cell cycle progression from the G1to the S phase.[25] An activity of CDK4/6 is regulated via different signaling pathways, including synergistic actions between HER2 and HR-related signalization networks.[25] Moreover, it has been noted that CDK4/6 inhibition can overcome acquired resistance to anti-HER2 therapies.[25] Recently, CDK4/6 inhibitors, abemaciclib and palbociclib, have been explored in clinical trials, in combination with aromatase inhibitors (AIs) or with an ER down-

regulator – fulvestrant in women with metastatic BC.[25]

For instance, abemaciclib, as is a selective CDK4/6 inhibitor (more potent against CDK4 than CDK6), is approved for monotherapy after progression on ET and previous CHT in patients with metastatic BC.[26] Abemaciclib is also approved in combination with ET in an initial setting and after progression on ET with fulvestrant.[27] The use of CDK4/6 inhibitors has been investigated in combination with HER2-targeted therapy and ET, including patients with HER2-positive and ER-positive metastatic BC.[25, 28] In particular, the MonarcHER trial (phase 2, NCT02675231) has explored the role of abemaciclib with trastuzumab in women with pretreated metastatic BC, and the PATINA trial (phase 2, NCT02947685) has investigated the benefits of adding palbociclib to trastuzumab, pertuzumab and an aromatase inhibitor (AI) (after an application of standard first-line therapy) in patients with HER2-positive metastatic BC (Table 1).[29, 30]

It should be underscored that Cyclin D1-CDK4 pathway can mediate resistance to HER2-targeted therapies. Notably, targeting resistant BC cells with CDK 4/6 inhibitors resensitizes them to anti-HER2 therapy and postpones tumor recurrence in HER2-driven BCs.[25, 28]

However, future trials are needed to precisely assess the efficacy and safety of combined HER2 and CDK4/6 inhibition in patients with HER2-positive BC.

Conclusion

Although the use of HER2-targeted therapies has remarkably changed the outcomes of numerous patients with HER2-positive advanced or metastatic BC, the majority of such women may still experience malignant progression, arriving at the stage, in which there is no approved HER2-targeted treatments that would control their malignancy. Fortunately, the rapid development of some innovative anti-HER2 therapies, such as margetuximab (Fc-engineered region mAb), trastuzumab deruxtecan (very potent ADC), and tucatinib (highly selective TKI), is going to expand future clinical horizons of effective therapies for patients with HER2-positive metastatic BC.

The underlying mechanisms of resistance to anti-HER2 therapies and compensatory communication pathways are very complex, and a wide spectrum of resistance modalities can coexist even within the single cell. In this aspect, combinations of anti-HER2 treatments that act in concert with novel PI3K/AKT/mTOR inhibitors and CDK4/6 inhibitors may be considered as potential strategies to combat the acquired resistance to treatment. Moreover, it has been reported that some recently developed bispecific antibodies (monoclonal antibodies targeting two different epitopes) are able to concurrently suppress multiple HER signaling pathways (including the HER3). Since HER2-positive BC is characterized by some degree of immunogenicity (that can be augmented by the use of anti-HER2 mAbs), the combination of trastuzumab and immunotherapy can also be considered, depending on the individual patient's clinical context. In addition, the development of biomarkers of therapeutic efficacy is going to be crucial for a precise selection of the most appropriate candidates for the novel anti-HER2 therapies and monitoring of their implementation among women suffering from HER2-positive metastatic BC.

Many innovative treatment strategies have recently been investigated in clinical trials, adding some optimism to this challenging area. However, further research is certainly needed to fulfill these unmet needs. Furthermore, to effectively reshape the therapeutic landscape of metastatic BC, the multidisciplinary team collaboration, as well as a respectful acknowledgment of the patient's

goals and preferences, need to be incorporated into the comprehensive care plan. Hopefully, these combined efforts will help overcome treatment resistance and achieve better survival and QoL of the patients with HER2-positive metastatic BC.

Disclosures

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References

1. Rimawi MF, Schiff R, Osborne CK. Targeting HER2 for the treatment of breast cancer. Annu Rev Med 2015;66:111–28. [CrossRef]
2. Larionov AA. Current therapies for human epidermal growth factor receptor 2-positive metastatic breast cancer patients. Front Oncol 2018;8:1–17. [CrossRef]
3. Rugo HS, Im SA, Wright GL, et al. SOPHIA primary analysis: A phase 3 (P3) study of margetuximab (M) + chemotherapy (C) versus trastuzumab (T) + C in patients (pts) with HER2+ metastatic (met) breast cancer (MBC) after prior anti-HER2 therapies (Tx). Journal of Clinical Oncology 2019 37:15_suppl, 1000. [CrossRef]
4. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, Andre F. DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020;382:610–21. [CrossRef]
5. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2019.
6. Wilks ST. Potential of overcoming resistance to HER2-targeted therapies through the PI3K/Akt/mTOR pathway. Breast 2015;24:548–55. [CrossRef]
7. Mishra P, Patel H, Alanasi S. Yuan L, Garrett JT. HER3 signaling

and targeted therapy in cancer. Oncol Rev 2018;355:45–62.
8. Pegram MD, Zong Y, Yam C, Goetz MP, Moulder SL. Innovative Strategies: Targeting Subtypes in Metastatic Breast Cancer. Am Soc Clin Oncol Educ Book 2018;38:65–77. [CrossRef]
9. Rinnerthaler G, Gampenrieder SP, Greil R. HER2 directed antibody-drug-conjugates beyond T-DM1 in breast cancer. Int J Mol Sci 2019;20:1–17. [CrossRef]
10. Tamura K, Tsuntani J, Takahashi S. et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. Lancet Oncol 2019;20:816–26.
11. Banerji U, van Herpen CML, Saura C, Thistlethwaite F, Lord S, Moreno V, et al. Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. Lancet Oncol 2019;20:1124–1135. [CrossRef]
12. Trail PA, Dubowchick GM, Lowinger TB. Antibody drug conjugates for treatment of breast cancer: novel targets and diverse approaches in ADC design. Pharmacol Ther 2018;181:126–42.
13. Kohrt HE, Houot R, Weiskopf K, et al. Stimulation of natural killer cells with a CD137-specific antibody enhances trastuzumab efficacy in xenotransplant models of breast cancer. J Clin Invest 2012;122:1066–75. [CrossRef]
14. Pegram MD. Tumor biology trumps anatomy in breast cancer brain metastases. Oncology (Williston Park) 2012;26:666–70.
15. Saura C, Oliveira M, Feng Y-H, Dai M-S, Hurvitz SA, Kim S-B. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 1002-1002. DOI: 10.1200/JCO.2019.37.15_suppl.1002. [CrossRef]
16. Guerrero-Zotano A, Mayer IA, Arteaga CL. P3K/AKT/mTOR: role in breast cancer progression, drug resistance, and treatment. Cancer Metastasis Rev 2016;35: 515–24. [CrossRef]
17. Hurvitz SA, Andre F, Jiang Z, Shao Z, Mano MS, Neciosup SP, et al. Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial. Lancet Oncol 2015;16:816–29.
18. André F, O'Regan R, Ozguroglu M, Toi M, Xu B, Jerusalem G. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014;15:580–91. [CrossRef]
19. Gourd E. Pyrotinib shows activity in metastatic breast cancer. Lancet Oncol 2017;18: e643. [CrossRef]
20. Ma F, Ouyang Q, Li W, et al. Pyrotinib or Lapatinib Combined With Capecitabine in HER2-Positive Metastatic Breast Cancer With Prior Taxanes, Anthracyclines, and/or Trastuzumab: A Randomized, Phase II Study. J Clin Oncol 2019. [CrossRef]
21. Park YH, Lee KH, Sohn JH, et al. A phase II trial of the pan-HER inhibitor poziotinib, in patients with HER2-positive metastatic breast cancer who had received at least two prior HER2-directed regimens: results of the NOV120101-203 trial. Int J Cancer 2018;143:3240–7. [CrossRef]
22. Chia S, Bedard PL, Hilton J, Amir E, Gelmon K, Goodwin R, et al. A Phase Ib Trial of Durvalumab in Combination with Trastuzumab in HER2-Positive Metastatic Breast Cancer (CCTG IND.229). Oncologist 2019;24:1439–45. [CrossRef]
23. Loi S, Giobbie-Hurder A, Gombos A, et al. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial. Lancet Oncol 2019;20:371–82. [CrossRef]
24. Emens LA, Esteva FJ, Beresford M, Saura C, De Laurentiis M, Kim S-B. Overall survival (OS) in KATE2, a phase II study of programmed death ligand 1 (PD-L1) inhibitor atezolizumab (atezo)+trastuzumab emtansine (T-DM1) vs placebo (pbo)+T-DM1 in previously treated HER2+ advanced breast cancer (BC). Annals of Oncology 2019; Vol. 30 Supplement 5, Page v104.
25. Goel S, Wang Q, Watt AC, et al. Overcoming therapeutic resistance in HER2-positive breast cancers with CDK4/6 inhibitors. Cancer Cell 2016;29:255–69. [CrossRef]
26. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. Clin Cancer Res 2017;23:5218–24. [CrossRef]
27. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: A randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer 2019;5. [CrossRef]
28. Brandão M, Pondé NF, Poggio F, et al. Combination therapies for the treatment of HER2-positive breast cancer: current and future prospects. Expert Rev. Anticancer Ther 2018;18:629–49.
29. Tolaney SM, Wardley AM, Zambelli S, et al: MonarcHER: A randomized phase II study of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with HR+, HER2+ advanced breast cancer. ESMO Congress 2019. Abstract LBA23. Presented September 28,2019. [CrossRef]
30. Loibl S, Metzger O, Mandrekar SJ, Mundhenke C, Seiler S, Valagussa P, et al. PATINA: A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy (ET) vs. Anti-HER2 Therapy + ET after Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer (MBC). Annals of Oncology 2018; 29 (suppl_8): viii90-viii121. [CrossRef]