Cancer Control
Volume 29: 1–7

DOI: 10.1177/10732748221106267
journals.sagepub.com/home/ccx
SAGE

Systemic Treatments for Metastatic Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Old Certainties and New Frontiers

Alessandro Rizzo, MD[1], Antonio Cusmai, MD[1], Raffaella Massafra, PhD[2], Samantha Bove, PhD[2], Maria Colomba Comes, PhD[2], Annarita Fanizzi, PhD[2], Gennaro Gadaleta-Caldarola, MD[3], Donato Oreste, MD[4], Alfredo Zito, MD[5], Francesco Giotta, MD[6], Vito Lorusso, MD[6], and Gennaro Palmiotti, MD[1]

Abstract

Epidermal growth factor receptor 2 (EGFR2, also known as HER2) overexpression and/or amplification confers a more aggressive clinical behavior but also represents a therapeutic opportunity for targeted therapies in breast cancer (BC). Over the last 2 decades, the prognosis of HER2-positive metastatic BC patients has improved due to the introduction of anti-HER2 agents including trastuzumab and novel, emerging drugs and combinations such as trastuzumab deruxtecan and tucatinib – trastuzumab - capecitabine. Herein, we provide a critical overview of current clinical recommendations and emerging treatment options for metastatic HER2-positive BC, especially focusing on recently presented and published clinical trials in this setting.

Keywords

breast cancer, metastatic breast cancer, trastuzumab deruxtecan, human epidermal growth factor receptor 2-positive, trastuzumab emtansine, tucatinib

Received April 15, 2022. Received revised May 10, 2022. Accepted for publication May 23, 2022.

Introduction

Breast cancer (BC) includes a set of malignancies with different biological and clinicopathological features, and BC remains the most frequent malignancy in women, accounting for 1 each 4 cancer cases.[1] To overcome this diversity, the last decades have seen the emerging of several classifications of BCs, with the aim of helping disease diagnosis and treatment, and improving prognosis.[2] Among these, a landmark classification identified 5 different BC subtypes: luminal A, normal-like, luminal B, triple-negative, and human epidermal growth factor receptor 2 (EGFR2, also known as HER2) – enriched tumors (Figure 1).[3] As regards the latter, HER2 is overexpressed and/or amplified in approximately 10-15% of all BCs, with HER2 overexpression/amplification conferring an aggressive behavior but also a therapeutic opportunity for targeted therapies.[4,5] Of note, in the locally advanced and metastatic settings, the prognosis of HER2-

[1]Struttura Semplice Dipartimentale di Oncologia Medica per la Presa in Carico Globale del Paziente Oncologico "Don Tonino Bello", I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco, Bari, Italy
[2]Struttura Semplice Dipartimentale di Fisica Sanitaria, I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco, Bari, Italy
[3]Medical Oncology Unit, 'Mons. R. Dimiccoli' Hospital, Barletta, Azienda Sanitaria Locale Barletta, Italy
[4]Radiology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Tumori Giovanni Paolo II, Bari, Italy
[5]Unità Operativa Complessa di Anatomia Patologica, I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco, Bari, Italy
[6]Unità Operativa Complessa di Oncologia Medica, I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco, Bari, Italy

Corresponding Author:
Alessandro Rizzo, Struttura Semplice Dipartimentale di Oncologia Medica per la Presa in Carico Globale del Paziente Oncologico "Don Tonino Bello", I.R.C.C.S. Istituto Tumori "Giovanni Paolo II", Viale Orazio Flacco 65, 70124 Bari, Italy.
Email: rizzo.alessandro179@gmail.com

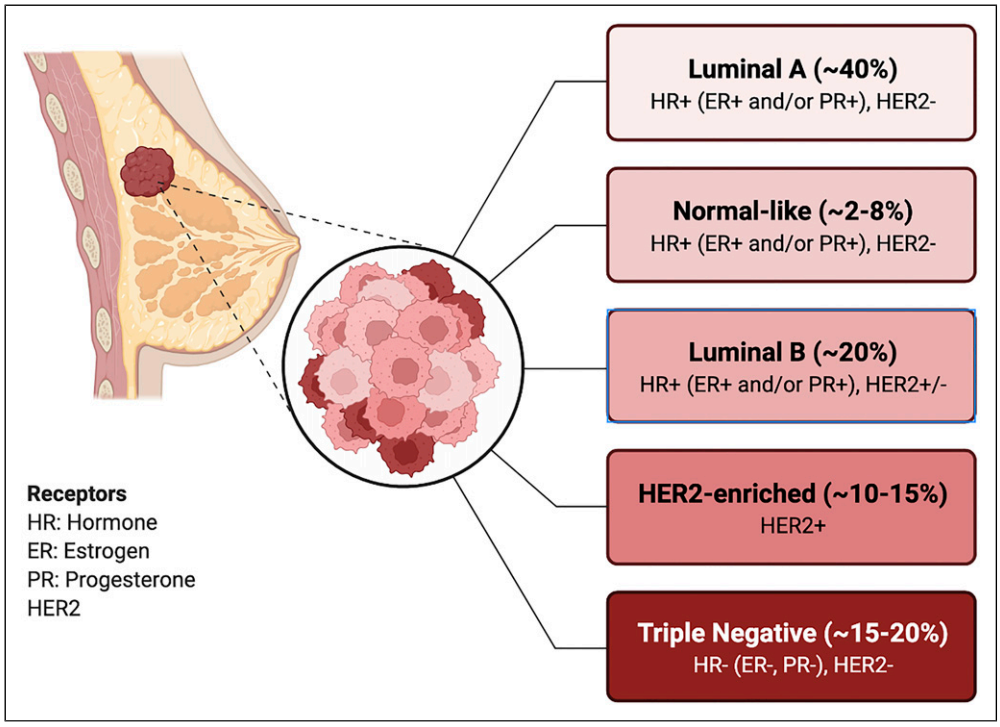

Figure 1. Schematic figure summarizing breast cancer subtypes based on their expression of hormone receptors, Ki-67, and the receptor tyrosine kinase HER2. Luminal A represents the most prevalent subtype and has low levels of Ki-67. HER2-enriched tumors present amplification of overexpression of receptor HER2, and have a faster growth compared with luminal subtypes. Triple negative tumors are the most aggressive subtype, occurring more often in younger patients.
Abbreviations: ER: estrogen receptor; PR: progesterone receptor; HER2: epidermal growth factor receptor 2.

positive BC patients has notably improved following the introduction of anti-HER2 agents including trastuzumab and novel drugs and combinations.[6,7] Classically, patients are eligible for HER2-directed treatments if they have HER2-positive disease, defined as follows: 1) immunohistochemical stain of 3+, defined as uniform intense membrane staining for HER2 in 10% or more of tumor cells, or 2) a HER2/chromosome enumeration probe 17 (CEP17) fluorescent in situ hybridization amplification ratio ≥ 2.0 and HER2 copy number signals/cell ≥ 4.

In the current review, we provide an overview of the current state of art and the emerging treatment options in the systemic treatment of HER2-positive advanced BC, especially focusing on recently presented and published clinical trials. We performed a research on Pubmed/Medline, Cochrane library and Scopus using the keywords "breast cancer" OR "HER2-positive breast cancer" AND "trastuzumab" OR "trastuzumab deruxtecan" OR "tucatinib" OR "pertuzumab" OR "trastuzumab emtansine" OR "margetuximab" OR "pyrotinib".

First-Line Treatment

The Beginning of the HER2 "Trail" in Advanced Breast Cancer

In March, 2001, Slamon and colleagues published on The New England of Medicine the results of a practice-changing phase III trial exploring the role of first-line chemotherapy plus trastuzumab vs chemotherapy alone in HER2-positive BC patients with metastatic disease.[8,9] According to the study design of this trial, chemotherapeutic regimens used as front-line treatment included doxorubicin/epirubicin and cyclophosphamide or paclitaxel[8]; of note, the authors highlighted the association of trastuzumab plus chemotherapy with a statistically significant and clinically meaningful benefit in terms of time to disease progression (7.4 months vs 4.6 months for chemotherapy alone; $P < .001$), objective response rate (ORR) (50% vs 32%; $P < .001$), and 1-year survival (25.1 months vs 20.3 months, respectively; $P = .046$).[8,9] In addition, evidence also suggested that overall survival (OS) was longer in BC patients receiving up-front trastuzumab – chemotherapy compared with subjects treated with sequential administration. Following these historical, landmark results, the United States (US) Food and Drug Administration (FDA) approved the use of trastuzumab as first-line treatment in HER2-positive BC patients with metastatic disease.[10,11]

More recently, the CLEOPATRA trial explored the role of pertuzumab plus trastuzumab plus docetaxel as first-line treatment for metastatic HER2-positive BC, establishing a new standard of care. The median OS was 56.5 months in the group receiving the pertuzumab combination, as compared with 40.8 months in the group receiving the placebo combination (Hazard Ratio [HR] favoring the pertuzumab group,

.68; 95% CI, .56 to .84; P < .001).[12,13] In this phase III study, the addition of pertuzumab to trastuzumab and docetaxel resulted in an increased median progression-free survival (PFS) of 18.5 months vs 12.4 months without pertuzumab, with an acceptable safety profile.[12] These results led to the FDA approval of the combination treatment with pertuzumab, trastuzumab, and docetaxel for metastatic HER2-positive, treatment-naïve, BC patients. Of note, the final analysis of CLEOPATRA trial highlighted that the OS benefit provided by pertuzumab, trastuzumab, and docetaxel was maintained following a median of more than 8 years of follow-up. Similarly, the analysis reported no increase in cardiac toxic effects for the triplet compared with trastuzumab – docetaxel.[12]

Current Recommendations: Front-Line Trastuzumab – Pertuzumab – Docetaxel

Based on these premises, the most updated international guidelines recommend the dual blockade with trastuzumab – pertuzumab plus docetaxel as the first-line standard in treatment-naïve HER2-positive BC patients with metastatic disease, regardless of hormone receptor status.[14,15] Docetaxel should be given for at least 6 cycles, if tolerated, followed by maintenance trastuzumab and pertuzumab until disease progression; after completing at least 6 cycles of upfront concomitant chemotherapy, endocrine treatment may be added to trastuzumab and pertuzumab maintenance therapy for patients with HER2-positive, hormone-receptor positive tumors.[14,15] In case of significant comorbidities, advanced age, and/or poor performance status in BC patients with hormone-receptor positive disease, endocrine treatment combined with a HER2-targeted therapy may be used. Lastly, the use of single-agent endocrine therapy without an anti-HER2 agent is not routinely recommended unless cardiac disease could preclude the safe use of HER2-directed treatments.

Second-Line Treatment

EMILIA Trial: Designing a New Standard of Care

In the phase III EMILIA trial, 991 patients with HER2-positive advanced BC and which were previously treated with trastuzumab and taxane were randomized to 2 treatments: the antibody-drug conjugate ado-trastuzumab emtansine (T-DM1) or lapatinib plus capecitabine.[16,17] T-DM1 is an antibody-drug conjugate (ADC) incorporating the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of emtansine, a microtubule-inhibitory agent. According to the results of this study, T-DM1 was shown to significantly prolong median PFS (9.6 months vs 6.4 months in the experimental and the control arm, respectively (HR, .65; 95% CI 0.55 to .77; P < .001) and median OS (30.9 months vs 25.1 months, respectively (HR, .68; 95% CI, .55 to .85; P < .001). The ORR was higher with T-DM1 (43.6%, vs 30.8% with lapatinib plus capecitabine; P < .001); in addition, T-DM1 was associated with a better safety profile compared with lapatinib plus capecitabine.[16,17] Based on the results of the practice-changing EMILIA phase III trial, the FDA approved T-DM1 for treatment of previously treated patients with metastatic HER2-positive BC. Of note, the final OS analysis – including patients who were allowed to crossover from control to T-DM1 - confirmed that median OS was significantly prolonged with T-DM1 compared with lapatinib plus capecitabine (29.9 months vs 25.9 months, respectively).[18] From the publication of EMILIA on, T-DM1 has been established as standard second-line treatment for BC patients with metastatic HER2-positive disease.

Trastuzumab Deruxtecan: A Rock in the Pond

In recent years, we have witnessed the development and testing of several novel HER2-targeted treatments, which have attracted the attention of the BC medical community. Among these, trastuzumab deruxtecan has surely represented a novelty of great interest. This agent is an antibody-drug conjugate containing the humanized anti-HER2 IgG1 trastuzumab which is covalently linked to the topoisomerase I inhibitor deruxtecan.[19,20] Following promising preclinical results, trastuzumab deruxtecan has been assessed in the open-label, phase II DESTINY-Breast01 trial including 184 HER2-positive metastatic BC patients who had received a median of 6 previous treatments[21]; this patient population was treated trastuzumab deruxtecan (5.4 mg/kg) every 3 weeks, achieving an overall response rate (ORR) of 60.9%, a complete response rate of 6.0%, and an impressive disease control rate (DCR) of 97.3%.[21,22] Median duration of response (DOR) was 14.8 months and median PFS of 16 months. However, interstitial lung disease represented an issue in this trial, with this adverse event of special interest which was observed in 25 patients (13.6%); of note, 4 patients (2.2%) experienced grade 5 interstitial lung disease and died due to this toxicity.[23]

Following these results, trastuzumab deruxtecan has been approved for treatment of patients with metastatic HER2-positive BC who have received 2 or more prior anti-HER2-based regimens.

More recently, trastuzumab deruxtecan has been tested also as second-line treatment, and this agent has been compared with T-DM1 in the DESTINY-Breast03 phase III trial enrolling BC patients with unresectable or metastatic HER2-positive BC who has been previously treated with trastuzumab and a taxane in the advanced/metastatic setting. The results of this study were previously presented at ESMO 2021 and have been recently published by Cortes and colleagues on the New England Journal of Medicine.[24] Of note, the 12-month PFS rate was 75.8% with trastuzumab deruxtecan vs 34.1% with T-DM1, with a HR for progression or death from any cause of .28 (95% Confidence Interval .22 to .37; P < .001)[24]; median PFS was not reached for the experimental arm while it was 6.8 months for T-DM1. However, it is worth noting that

serious drug-related toxicities were reported in 10.9% of patients treated with trastuzumab deruxtecan (versus 6.1% of patients receiving T-DM1).[24]

Other Treatment Options: Tucatinib and "His Brothers"

A plethora of novel treatments have emerged in the landscape of HER2-positive disease. In 2020, the FDA approved the use of the orally bioavailable, small molecule tyrosine kinase inhibitor (TKI) tucatinib. This highly selective HER2-targeted agent is currently indicated in combination with trastuzumab and capecitabine for treatment of BC patients with advanced unresectable or metastatic HER2-positive BC, including those with brain metastases and who have received one or more prior anti-HER2-based regimens in the metastatic setting.[25] The approval of tucatinib was based on the results of the phase III HER2CLIMB trial published by Murthy and colleagues; in this international, multicenter study, the investigators randomized 612 heavily pretreated BC patients to receive trastuzumab and capecitabine plus either tucatinib (300 mg, orally, twice daily) or placebo.[26,27] The study included a widely varied patient population, ranging from patients with previously treated stable brain metastases, untreated brain metastases not needing immediate local therapy, previously treated progressing brain metastases not needing immediate local therapy, and BC patients with no evidence of brain metastases. Stratification factors were the presence of brain metastases, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0 or 1, and geographical region (US, Canada or rest of the world).[26,27] The HER2CLIMB study met all primary and secondary endpoints at the first interim analysis, and importantly, the secondary endpoint of PFS in BC patients with brain metastases was met, with risk of progression or death which was reduced by 52% in this patient population (HR, .48; 95% CI, .34 to .69; P < .001). Median PFS in the tucatinib arm and the control arm was 7.8 months and 5.6 months, respectively, while median OS 21.9 months and 17.4 months, respectively.[26,27] Of note, median PFS for BC patients with baseline brain metastases in the tucatinib-treated group was 7.6 months, compared with 5.4 months in patients without tucatinib. The updated results of HER2-CLIMB have confirmed these data, with an OS improvement of 9.6 months in patients with active brain metastases and 5.2 months in those with stable brain metastases provided by tucatinib – trastuzumab – capecitabine.[28]

Another HER2-targeted agent, neratinib, was approved by the US FDA in February 2020 in combination with capecitabine for patients who have received 2 or more prior anti-HER2-based regimens in the metastatic setting, following the results of the NALA trial.[29,30] In this multicenter, randomized, open-label study, 621 BC patients were randomized to neratinib (240 mg orally, once daily, on days 1-21) plus capecitabine (750 mg/m^2 given orally twice daily on days 1-14 for each 21-day cycle) or lapatinib (1250 mg orally, once daily, on days 1-21) plus capecitabine (750 mg/m^2 given orally twice daily on days 1-14 for each 21-day cycle).[29,30] PFS analysis statistically favored neratinib – capecitabine, with patients receiving the experimental combination showing a median PFS of 5.6 months vs 5.5 months for those receiving lapatinib plus capecitabine (HR .76, P = .0059). Conversely, median OS was 21 months for patients receiving neratinib – capecitabine compared to 18.7 months for those treated with lapatinib plus capecitabine, without reaching the statistical significance (P = .2). The ORR was 32.8% vs 26.7%, respectively.[29,30]

Pyrotinib has been recently explored in BC patients with brain metastases.[31] This irreversible dual pan-ErbB receptor TKI was assessed in the phase II PERMEATE trial, whose results have been recently published on The Lancet Oncology, reporting an ORR of 74.6% in the central nervous system.[32] However, patients experiencing disease progression following stereotactic radiation therapy or whole-brain radiotherapy presented an overall lower ORR (42.1%). In addition, median PFS was significantly longer in the radiation therapy – naïve cohort (12.1 months) compared with the radiotherapy cohort (5.6 months). In terms of treatment-related adverse events, the most frequently observed grade 3 toxicity was diarrhea (23.1%), followed by hematological toxicities, including decreased neutrophil cell count (12.8%), decreased white blood cell count (12.8%), and anaemia (9%).[32]

Another promising agent is margetuximab, which has already been tested in other HER2-positive solid tumors, including metastatic gastric adenocarcinoma.[33] As regards metastatic HER2-positive BC, margetuximab was approved by the US FDA in December 2020 as part of a combinatorial regimen with chemotherapy for patients who have received 2 or more prior HER2-targeted therapies, at least one of which for metastatic disease.[33] The approval was based on the results of the SOPHIA study[34]; in this multicenter, randomized, open-label trial, 536 HER2-positive BC patients who had received previous HER2-targeted therapies were randomized to margetuximab plus chemotherapy or trastuzumab – chemotherapy. Stratification factors of this study included the number of lines of therapy in the advanced/metastatic setting (equal or less than 2, more than 2), the chemotherapy choice (gemcitabine, eribulin, vinorelbine, or capecitabine), and the number of metastatic sites (equal or less than 2, more than 2). The margetuximab arm showed a median PFS of 5.8 months vs 4.9 months in the control arm (HR .76; P = .033), with an ORR of 22% and 16%, respectively.[34] The most commonly reported treatment-related adverse events included fatigue, nausea, and diarrhea.

HER2-Positive Disease: A Critical Overview and Open Questions

As previously stated, the most up-to-date international guidelines recommend the CLEOPATRA-like regimen with

pertuzumab – trastuzumab – taxane as first-line treatment, regardless of hormone receptor status. The latest international guidelines have reported a paradigm shift for previously treated BC patients, following the presentation of the DESTINY-Breast03 establishing trastuzumab deruxtecan as second-line treatment in this setting.[35] As reported, the results of CLEOPATRA have been immediately practice-changing, due to the superiority of the dual HER2 blockade over single HER2 blockade. In the second-line setting, the – previous – standard was based on EMILIA, showing the survival advantage provided by T-DM1 over capecitabine – lapatinib.

However, we have recently seen the development and emerging of a novel agent, which has revolutionized previous algorithms: trastuzumab deruxtecan. Of note, this ADC has notable differences with T-DM1, with a high drug-to-antibody ratio and a different payload. In addition, trastuzumab deruxtecan has a tumor-selective cleveable linker and there is evidence of a bystander anti-tumor effect. The recently published DESTINY-Breast03 study has shown a very high ORR for trastuzumab deruxtecan (79.7% vs 34.2% of T-DM1), something that strongly supports the use of this agent in previously treated patients. In addition, the study has seen an unprecedented PFS benefit for the experimental arm, with a median PFS of 75.8 months vs 34.1 months, respectively. When looking at subgroup analyses, it is worth noting that the benefit provided by trastuzumab deruxtecan over T-DM1 is consistent across several clinically meaningful subgroups, and thus, it has been showed regardless of prior pertuzumab treatment, hormone receptor status, visceral disease, prior lines of therapy, and presence of brain metastases.

At the same time, deruxtecan-related adverse events should be carefully considered and discussed. In the phase II DESTINY-Breast01 trial, 25 cases of interstitial lung disease were highlighted, something that has raised some concerns.[21] Of note, among the total 25 events, median time to investigator-reported onset was 193 days and ranged from 42 to 535 days; 17 out of 20 patients with interstitial lung disease graded as equal or more than 2 received corticosteroids.[21] As previously reported, 4 patients died due to this adverse event of special interest, with grade 5 toxicity occurring from 9 to 60 days after diagnosis of interstitial lung disease.[21] These 4 cases of grade 5 adverse events, representing the 2.2% of all included patients, have been largely discussed in the BC medical community. However, the safety results from the DESTINY-Breast03 trial have been quite reassuring.[24] In fact, only 2 cases (0.8%) of grade 3 interstitial lung disease were reported, with no cases of grade 4 and/or 5 toxicities.[24] Several recommendations remain to be considered, including close monitoring for symptoms as well as starting steroids as soon as interstitial lung disease is suspected.[36,37]

Certainly, we are witnessing a therapeutic revolution in metastatic HER2-positive disease, with several novel agents "on the block"; at the same time, in everyday clinical practice it is necessary to remember that "older" therapies are still worthwhile, especially in case of lack of reimbursement or access to novel agents. An example is represented by trastuzumab plus lapatinib, which has been shown to be particularly effective in hormone receptor negative patients, as well as chemotherapy plus lapatinib. Another key point to consider is represented by immunotherapy. As immune checkpoint inhibitors are changing the paradigm of anticancer for treatment, it arises as another therapeutic option for BC patients, including those with HER2-positive disease, where several trials are ongoing.[38,39]

Conclusions

HER2-positive disease remains an aggressive subtype of BC, whose advances in treatment have been notable but still more efforts need to be done. The search for novel targeted therapies has recently been extremely intense, with trastuzumab deruxtecan and tucatinib leading the way. Unfortunately, HER2-positive disease remains an unmet medical need, with also the design of clinical trials demanding for improvement, due to the frequent inclusion of distinct endpoints and different population sizes, something that makes it difficult to compare and analyze the results. Ongoing clinical trials assessing novel agents and combinations have the potential to further modify this changing scenario.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

ORCID iD

Alessandro Rizzo https://orcid.org/0000-0002-5257-8678

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