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HER2 Positive Breast Cancer Therapy - A Challenging and Continuously Moving Pathway – A Narrative Literature Review

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ABSTRACT

Background: Alteration of the expression of human epidermal growth factor receptor-2 gene as an oncogenic pathway in breast cancer was first explored in the 1980s. Since then, tremendous progress has been made in treating HER2-positive breast cancer.

Methods: We performed a narrative type review of the existing literature using as a starting point the PubMed database, using keywords, with the search being refined later and the relevant articles being selected. As the approaches to the topic under discussion were different in various studies, we were convinced of the inappropriateness of a meta-analysis. As a secondary method of analysis, we evaluated the bibliography of each of the selected studies and from this we identified other publications of interest.

Results: At present, there are three major classes of FDA-approved anti-HER2 agents: monoclonal antibodies (Trastuzumab, Pertuzumab and Margetuximab), TKIs (Lapatinib, Neratinib and Tucatinib) and antibody-drug conjugates (T-DM1 and T-DXd). The treatment of HER2+ breast cancer has suffered some changes in the last few years. If in 2018, progression under first-line treatment with taxane-trastuzumab/pertuzumab and second line with T-DM1 was a big challenge, and it was up to the oncologist to choose from lapatinib-capecitabine, trastuzumab-lapatinib or different chemotherapeutic agents depending on toxicities and therapies available in the country, nowadays we have a new third- and fourth-line FDA approved standard, which consists of tucatinib-trastuzumab-capecitabine and trastuzumab-deruxtecan.

Conclusion: The question of how to improve novel therapies to treat HER2-positive disease remains a topic of discussion in the future, because we are only getting closer to an optimal version of treatment for HER2+ breast cancer, hoping that the introduction of new drugs and the establishment of new indications for old drugs will allow us to standardize the treatment of these patients.

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INTRODUCTION

Over-expression and amplification of human epidermal growth factor receptor-2 (HER2, ErbB2) were identified as a pathway in the development of breast cancer (BC) for the first time by Urlich in the 1980s. The breakthrough discovery that led to the

development of trastuzumab was the ability of tumor necrosis factor-alpha (TNF-α) to inhibit tumor growth and the fact that it was repressed by the activation of growth factor receptors.[1] The conclusion was that the production of growth factors by the malignant cells also serves as a protective mechanism against host immune surveillance, not just for the promotion of proliferation (autocrine growth factor).[2] Based on this observation, Urlich and Slamon made a series of correlations that led to the FDA approval of trastuzumab in 1998.

The over-expression of the ErbB2 oncogene is present in a variety of cancers. The anti-HER2 therapy is commonly used for the treatment of breast tumors, where mutation is present in 15 to 20 % of the cases.[3] Before the approval of trastuzumab (Herceptin), ErbB2 positive testing was used only as a negative prognostic factor, but once Herceptin became available, the paradigm changed completely, transforming HER2+ BC into a treatable malignancy.[4]

However, the significant improvements in survival observed with trastuzumab in HER2+ BC did not amount to a cure, as many hoped, and further research on HER2-positive cancers led to the development of other therapeutic agents. Antibody-drug conjugates such as trastuzumab-emtansine (T-DM1), tyrosine kinase inhibitors (TKI) with small molecules such as lapatinib, neratinib and other monoclonal antibodies with different mechanisms of action, such as pertuzumab, have been developed and approved and are now commonly used.[5]

METHODS

To review the literature, first the Pub Med database was searched for randomized clinical trials (English only, years 1996-2021) of HER2-positive breast cancer patients who received anti-HER agents and for articles on the mechanisms of action of anti-HER agents. We investigated PubMed searching for the same keywords used in this study by performing a stepwise search considering the fact that the initial entry of more than two or three keywords often makes the search irrelevant for all keywords, but specific only for the first ones. This procedure allowed us a better filtering of the results in our opinion. Among the identified articles, we especially retained those that were available in full text, but some were available only in the abstract format which provided us with interesting results.

For the available full-text studies, we carefully went through the bibliography of each one, using it as a potential secondary source of information. The identified reference lists were further filtered for keywords related to new therapies in HER2-positive disease, mechanism of action, survival rates in advanced HER2-positive breast neoplasm.

The documentation for this literature review was carried out in the second half of 2021, with a total duration of approximately 4 months in the database investigation. In January 2022, the bibliography of the initially identified full-text studies was analyzed. In this way, we can affirm the validity of our results related to this final analysis we performed.

RESULTS

From the 1980s until now, research has evolved tremendously. Aberrant expression of epidermal growth factor family of receptors of tyrosine kinase is involved in the development of gastric cancer, BC, pulmonary non-small carcinoma and other malignancies, playing a crucial role in the regulation of proliferation, differentiation and migration of cells. The human EGFR family comprises four members: HER1 (EGFR), HER2, HER3 and HER4. Each member has an extracellular component, with four domains for ligand-binding and receptor dimerization, a transmembrane region and an intracellular tyrosine kinase domain.[6] The activation of HER requires a bound ligand. HER2 is constitutively available for dimerization and forms heterodimers with other ligand-activated HER receptors or homodimers in the cells which present over expressed HER2.[7] The dimerization of the receptor produces a conformational change, which will lead to the activation of the intracellular tyrosine kinase domain and the phosphorylation of the C-terminal tail, with activation of various signaling pathways. The most important pathways activated by the ErbB family are RAS/MAPK and PI3K/AKT, which lead to cell proliferation and angiogenesis.[8]

Anti-HER agents – mechanism of action

Slamon's monoclonal antibody was just the start. Significant progress has been made in the HER2 blockade. At present, there are three major classes of FDA-approved anti-HER2 agents: monoclonal antibodies (Trastuzumab, Pertuzumab and Margetuximab), TKIs (Lapatinib, Neratinib and Tucatinib) and antibody-drug conjugates (T-DM1 and T-DXd).

Trastuzumab has the ability to bind to the extracellular domain of HER2, which prevents the dimerization of the receptor and, additionally, induces antibody-dependent cellular cytotoxicity. Because the blockade is incomplete, another monoclonal antibody has been developed. Pertuzumab has the same mechanism of action, but it binds to a different epitope, leading to a much more efficient blockade. Margetuximab, a chimeric IgG1 monoclonal antibody, is the latest anti-HER2 agent approved by FDA. Basically, it has the same murine precursor as trastuzumab, but the Fc domain is created through bioengineering technology. The ultimate advantage is

the improved binding to CD16A, a stimulatory receptor found on the surface of macrophages and NK cells, which leads to increased antibody-dependent cellular cytotoxicity.[9,10]

The TKIs exhibit their properties at the intracellular level. Lapatinib inhibits the activation of signaling pathways of EGFR and HER2, especially MAPK, PI3K-AKT and PLCγ, by decreased phosphorylation of target receptors. Neratinib, another TKI used in the HER blockade, is known as a pan-inhibitor and interacts with EGFR, HER2 and HER4. Neratinib lowers the signal transduction and leads to cell cycle arrest in G1-S phase. In addition, neratinib can reverse the multidrug-resistance mediated through membrane-bound ATP transporters, which contributes to improved response to chemotherapy. The latest anti-HER2 TKI approved by FDA, Tucatinib, is a selective inhibitor of phosphorylation of ErbB2 and prevents the transduction of the signal, leading to growth inhibition and apoptosis of HER2-positive cells.[11,12]

The antibody-drug conjugates (ADCs) combine the anti-HER2 activity of trastuzumab with the cytotoxicity of the chemotherapy agents. Ado-trastuzumab emtansine (T-DM1) is a conjugate of trastuzumab with DM1, a cytotoxic anti-microtubule agent. T-DM1 binds to the HER2 receptor and the complex is internalized through endocytosis. The complex goes through proteolytic degradation, which will release the DM-1. The DM1 metabolites inhibit the assembly of the microtubules and lead to cell cycle arrest in the G2-M phase, resulting in the impossibility of mitosis and secondary apoptosis. The novel agent trastuzumab-deruxtecan combines trastuzumab with a derivate of camptothecin. The camptothecin binds to the DNA topoisomerase I, resulting in irreversible DNA damage, which will initiate the apoptosis process.[13]

What are the current options and when can we use them?

Besides the well-known trastuzumab, which has proved useful in both adjuvant and neoadjuvant settings, the addition of pertuzumab significantly improved the control of HER2-positive disease with higher differences in the high-risk groups: hormone receptor-negative group and lymph nodes positive group. The APHINITY trial demonstrated for the first time the efficacy of double HER2 blockade in the adjuvant setting and led to the FDA approval. The trial was double-blinded and randomized in two arms: pertuzumab plus trastuzumab and placebo plus trastuzumab (Table 1).

The treatment with pertuzumab plus trastuzumab increased disease-free survival [DFS; HR 0.81; 95% confidence interval (CI), 0.66–1.00; P ¼ 0.045], with an estimated 3-year invasive DFS rate of 94.1 versus 93.2%. The side effects were rare in both arms, with a higher rate of diarrhea in the pertuzumab arm (9.8 vs. 3.7%), especially during chemotherapy.[14] NeoSphere showed the superiority of Pertuzumab, Trastuzumab and Docetaxel over Trastuzumab and Docetaxel when used in the neoadjuvant setting. NeoSphere trial led to the reliable use of the double blockade (pertuzumab and trastuzumab), having as primary end-point the pathological complete response (pCR) rate in the breast (ypT0), which was accomplished in 29.0% of women treated with trastuzumab plus docetaxel (95% CI 20.6–38.5%), compared to 45.8% of women (n=107) treated with pertuzumab, trastuzumab and docetaxel (CI 36.1–55.7%) (P=0.0141)[15] (Table 1). The TRYPHENA trial supported the clinical benefit of Pertuzumab plus Trastuzumab, regardless of the chemotherapy backbone. The TRYPHAENA trial evaluated as primary end-point the safety and pCR rate in the breast and all patients enrolled received pertuzumab with chemotherapy.[16]

CLEOPATRA trial evaluated the benefit of the therapy with dual HER2 blockade in the first line in patients with HER2-positive metastatic breast cancer. All the enrolled patients received trastuzumab (weekly or every three weeks) and docetaxel with pertuzumab (every three weeks) or placebo. The objective response rate was 24.2%, and the clinical benefit rate was 50%. The progression-free survival (PFS) was elongated from 12.4 months to 18.5 months (hazard ratio [HR] for progression or death, 0.62; 95% CI, 0.51–0.75; P<0.001). Pertuzumab reduced the HR regardless of the utilization of adjuvant or neoadjuvant chemotherapy. The median overall survival (OS) was 56.5 months (95% CI, 49.3 to not reached) in the pertuzumab group versus 40.8 months (95% CI, 35.8–48.3) in the control group with an overall response rate of 80.2%.[17] There is a serious concern about resistance to trastuzumab and there were several studies that tried to overcome this resistance, as BOLERO1 trial. BOLERO1 consisted of adding Everolimus to the well-known trastuzumab + Paclitaxel combination in women with advanced HER2 positive disease. The logic was to attempt to sensitize PTEN-deficient tumors to trastuzumab by inhibiting mTOR resistance, but the trial showed a modest improvement in PFS, with significant toxicity.[18] BOLERO3 showed that adding Everolimus to Trastuzumab plus Vinorelbine in taxane-pretreated patients with advanced disease leads to a significant improvement of PFS. However, we must take into account the significant toxicity.[19]

Table 1. Independent trials

Name of Clinical trial		
The APHINITY trial	The trial was double-blinded and randomized in two arms: pertuzumab plus trastuzumab and placebo plus trastuzumab.	Demonstrated the efficacy of double HER2 blockade in the adjuvant setting. Pertuzumab plus trastuzumab increased disease-free survival, with a n estimated 3-year invasive DFS rate of 94.1 versus 93.2%.
NeoSphere trial	Usage of Pertuzumab, Trastuzumab and Docetaxel over Trastuzumab and Docetaxel when used in the neoadjuvant setting.	Reliably use of the double blockade (pertuzumab and trastuzumab), having as primary end-point the pathological complete response (pCR) rate in the breast.
The TRYPHENA trial	This trial evaluated as primary end-point the safety and pCR rate in the breast. All patients enrolled received pertuzumab with chemotherapy.	Supported the clinical benefit of Pertuzumab plus Trastuzumab, regardless of the chemotherapy backbone.
CLEOPATRA trial	Evaluated the benefit of the therapy with dual HER2 blockade in the first line in patients with HER2-positive metastatic breast cancer. Patients received trastuzumab (weekly or every three weeks) and docetaxel with pertuzumab (every three weeks) or placebo.	Objective response rate = 24.2%, clinical benefit rate = 50%. Progression-free survival (PFS) - elongated from 12.4 to 18.5 months. Median overall survival (OS) = 56.5 months in the pertuzumab group vs. 40.8 months in the control group with an overall response rate of 80.2%.
BOLEORO1 and BOLEORO3 trials	Trial tried to overcome the resistance to trastuzumab. Everolimus was added to the well-known trastuzumab + Paclitaxel combination in women with advanced HER2 positive disease.	BOLEORO1 - modest improvement in PFS, with significant toxicity. BOLERO3 - adding Everolimus to Trastuzumab plus Vinorelbine in taxane-pretreated patients with advanced disease leads to a significant improvement of PFS.
The MARRIANE trial	This trial evaluated T-DM1-containing regimens in the first line.	PFS or OS did not improve. The safety profile of T-DM1 was superior to the trastuzumab plus taxane arm. Fewer treatment discontinuations due to adverse events.
HER2CLIMB trial	Patients with HER2 positive metastatic BC, randomized in two arms: tucatinib + trastuzumab + capecitabine and placebo + trastuzumab + capecitabine. Patients with active or stable brain metastasis.	The median PFS for the first 480 patients enrolled: experimental arm 7.8 vs. 5.6 months in control arm. Good response in brain metastasis, with a PFS of 18.1 months.
SOPHIA trial	Compared margetuximab + chemotherapy with trastuzumab + chemotherapy in patients previously treated with minimum two anti-HER2 agents for metastatic BC.	Margetuximab + chemotherapy reduced risk of progression and death with 24% in a heavily pretreated population. Median PFS with margetuximab + chemotherapy was 5.8 vs. 4.9 months with trastuzumab + chemotherapy. Improved median OS (22% vs. 16%).
A meta-analysis, by Wang et al. (2020)	The meta-analysis included 11 studies and the subgroup analysis of combined-drug treatments.	The results were inconsistent. Suggests that neoadjuvancy with double blockade of HER2 + chemotherapy improves the pCR rate in HER2+ BC.
Phase II trial I-SPY 2	Assessed neratinib in the neoadjuvant setting.	Ad of neratinib to the standard neoadjuvant regimen - best results in HER2 positive and HR negative disease. Rate of primary end-point was higher in the experimental arm vs. the control arm (56 vs. 33%).
Phase II double-blinded KATE2 trial	Randomized patients with advanced HER2 positive BC, who previously received treatment with trastuzumab and a taxane, into two arms: trastuzumab-emtansine + atezolizumab and trastuzumab-emtansine + placebo.	Due to the increased number of side effects in patients on atezolizumab, the assigned arm was unmasked. Most common adverse effects: thrombocytopenia, increased AST and ALT, anemia and neutropenia. Serious adverse events - in 33% of atezolizumab vs. 19% of placebo. One patient on atezolizumab died due to hemophagocytic syndrome.

Trastuzumab emtansine (T-DM1) has been shown to be effective in metastatic HER2 positive disease. The phase III EMILIA trial, which compared the safety and efficacy of T-DM1 with lapatinib plus capecitabine in participants with HER2 positive ABC who previously received treatment with trastuzumab and taxane-based chemotherapy, showed a significant improvement in PFS, in the favor of T-DM1 (Table 2). The PFS improved from 6.4 months to 9.6 months.

More importantly, patients receiving T-DM1 showed prolonged OS (30.9 months vs. 25.1 months). The EMILIA study also demonstrated a better safety profile, with fewer grade 3 adverse events compared with the control group. In the light of the EMILIA trial results, T-DM1 is the preferred second-line therapy after treatment with trastuzumab and taxane-based chemotherapies.[20] A second phase III, open-label trial, TH3RESA, which compared T-DM1 with the treatment of physician's choice, showed that PFS was significantly improved with T-DM1 compared with the physician's choice (6.2 months vs. 3.3 months) (Table 2).

Table 2. Phase III trials

Clinical Trial		
The phase III EMILIA trial	Compared the safety and efficacy of T-DM1 with lapatinib plus capecitabine in participants with HER2 positive ABC who previously received treatment with trastuzumab and taxane-based chemotherapy.	Significant improvement in PFS, in favor T-DM1 (from 6.4 to 9.6 months). Patients receiving T-DM1 showed prolonged OS (30.9 vs. 25.1 months). Demonstrated a better safety profile, with fewer grade 3 adverse events compared with the control group.
TH3RESA trial- phase III, open-label trial	Compared T-DM1 with the treatment of physician's choice.	PFS significantly improved with T-DM1 compared with physician's choice (6.2 vs. 3.3 months). The OS analysis - significant longer survival with T-DM1 (22.7 vs. 15.8 months).
Phase III trials - KRISTINE	Designed to evaluate the efficacy and safety of T-DM1 + pertuzumab vs. trastuzumab + pertuzumab + chemotherapy (TCHP) in HER2+ early breast cancer, no previous treatment. Neoadjuvant treatment period, followed by surgery and an adjuvant treatment.	Study showed that the treatment used in the control arm is linked with a larger percentage of patients achieving pCR than in the experimental arm.
Phase III trials- KATHERINE	Evaluated the efficacy and safety of T-DM1 vs. trastuzumab as adjuvant therapy for patients with HER2+ early high-risk, who present residual tumor or axillary lymph nodes after neoadjuvant therapy.	After completion of neoadjuvancy and surgery, the risk of recurrence of invasive breast cancer or death decreases by 50% with adjuvant T-DM1 than with trastuzumab.
Phase III trials- KAITLIN (still ongoing)	Trial is comparing trastuzumab + pertuzumab + taxane following anthracyclines vs. T-DM1 + pertuzumab following anthracyclines as adjuvant treatment in operable HER2+ early BC.	This trial is estimated to be completed in 2024.
Phase 3 ExteNET trial	This study evaluated Neratinib in monotherapy for extended adjuvancy in patients with HER2 positive early BC who have been recurrence-free after completing 12 months trastuzumab adjuvant therapy.	Neratinib for extra 12 months significantly improved the prospect of iDFS (primary end-point) for two years compared with placebo Patients experienced fewer iDFS events than those in the control group. The benefit of neratinib was greater against HR-positive than HR negative.
Phase III NALA trial	Evaluates the response to neratinib plus capecitabine for the treatment of HER2 positive metastatic BC in patients previously treated with two or more anti-HER2 regimens.	Decreases the risk of disease progression and death by 34%, in comparison with lapatinib and capecitabine in HER2 positive BC and central nervous system metastases. Decreases the risk of disease progression and death by 34% vs. lapatinib and capecitabine.

The OS analysis proved a significantly longer survival with T-DM1 (22.7 months vs. 15.8 months).[21] The MARRIANE trial evaluated T-DM1-containing regimens in the first line. Even though neither PFS nor OS improved, the safety profile of T-DM1 was superior to that of the trastuzumab plus taxane arm, leading to fewer treatment discontinuations due to adverse events. Therefore, MARIANNE supported TDM1 as an alternative first-line treatment, as was presented at the 2017 ASCO Meeting. Additionally, It should be mentioned that in the case of patients in whom a therapeutic response was obtained,, the interval of the response was longer in the T-DM1 arm than in the trastuzumab plus taxane arm, resulting in the inclusion of T-DM1 as another first-line treatment option for metastatic patients who were not considered suitable for treatment with the preferred regimen of trastuzumab plus pertuzumab plus taxane.[22] T-DM1 was also evaluated in the neoadjuvant and adjuvant settings by the phase III trials KRISTINE, KAITLIN and KATHERINE. The KRISTINE study was the first trial involving T-DM1 to compare a neoadjuvant regimen for HER2+ BC that did not use classical systemic chemotherapy, replacing it with targeted agents. This trial was designed to evaluate the efficacy and safety of T-DM1 plus pertuzumab versus trastuzumab plus pertuzumab plus chemotherapy (TCHP) in HER2+ early breast cancer patients without previous treatment. The study included a neoadjuvant treatment period, followed by surgery and an adjuvant treatment period. The data showed that the treatment used in the control arm is linked with a larger percentage of patients achieving pCR than in the experimental arm.[23] The KATHERINE study has evaluated the efficacy and safety of T-DM1 versus trastuzumab as adjuvant therapy for patients with HER2+ early high-risk BC who present residual tumor in the breast or axillary lymph nodes after neoadjuvant therapy. The data show that after completion of neoadjuvancy and surgery, the risk of recurrence of invasive breast cancer or death decreases by 50% with adjuvant T-DM1 than with trastuzumab.[24] As a result, T-DM1 has been approved by the FDA for use as an adjuvant treatment for patients with HER2+ early BC who have residual disease after neoadjuvancy with trastuzumab and chemotherapy. The KAITLIN trial, still ongoing, is comparing trastuzumab plus pertuzumab plus taxane following anthracyclines versus T-DM1 plus pertuzumab following anthracyclines as adjuvant treatment in patients with operable HER2+ early BC. This trial is estimated to be completed in 2024.

Neratinib was evaluated in monotherapy in the phase 3 ExteNET trial (NCT00878709) for extended adjuvancy in patients with HER2 positive early BC who have been recurrence-free after completing 12 months of trastuzumab adjuvant therapy. Neratinib for extra 12 months significantly improved the prospect of iDFS (primary end-point) for two years compared with placebo. Patients in the neratinib arm experienced fewer iDFS events than those in the control group (70 vs. 109 events; HR 0.67, 95% CI 0.50–0.91; p=0.0091). The iDFS rate at two years was 93.9% (95% CI 92.4 – 95.2) in the neratinib group and 91.6% (90.0–93.0) in the placebo group. DFS was superior in the neratinib arm in comparison with the placebo arm (93.9% vs. 91.0; HR 0.63; p=0.0017). The benefit of neratinib was greater against HR-positive than HR negative BC [25]. The phase II trial I-SPY 2 also assessed neratinib in the neoadjuvant setting. Adding neratinib to the standard neoadjuvant regimen in patients with early BC presented the best results in patients with HER2 positive and HR negative disease. The rate of pCR (the primary end-point) was higher in the experimental arm when compared with the control arm (56 vs. 33%).[26]

What's new?

The analysis of the phase III NALA trial showed that Neratinib (Nerlynx) in combination with capecitabine decreases the risk of disease progression and death by 34%, in comparison with lapatinib and capecitabine in patients with HER2 positive BC and central nervous system metastases. The median PFS was 7.8 months, compared with 5.5 months in the experimental arm (HR 0.66; 95% CI, 0.41-1.05). The OS, which was the second end-point, did not present any differences between the two arms.[27] These findings led to the FDA approval in early 2020 of a new application for neratinib plus capecitabine for the treatment of HER2 positive metastatic BC in patients previously treated with two or more anti-HER2 regimens. A problem with the use of Neratinib is the digestive toxicity that was addressed in the CONTROL study presented at 2019 SABCS.

The newest TKI approved by FDA, tucatinib, was evaluated in the HER2CLIMB trial, which enrolled patients with HER2 positive metastatic BC and randomized them into two arms: tucatinib plus trastuzumab plus capecitabine and placebo plus trastuzumab plus capecitabine. The median PFS for the first 480 patients enrolled was 7.8 months (95% CI, 7.5–9.6 months) in the experimental arm and 5.6 months (95% CI 4.2–7.1 months) in the control arm [28]. Her2CLIMB also included patients with active and stable brain metastasis (a population subgroup with a poor prognosis), showing a good response in brain metastasis, with a PFS of 18.1 months. The analysis showed prolongation of OS in the M1 CNS subgroup for Tucatinib, Trastuzumab

and Capecitabine vs. Trastuzumab and Capecitabine (OS with HR= 0.49 p=0.004).[28]

Trastuzumab – deruxtecan (T-DXd, DS-8201) was recently approved by FDA for the treatment of unresectable/metastatic HER2-positive BC previously treated with at least two types of anti-HER2 agents. In the DESTINY-Breast01 phase II, trial patients with HER2 positive disease, with an average of six lines of treatment for metastatic disease, experienced a response rate of 60.9% and a PFS of 16.4 months (Table 3). After 12 months, 86.2% of the patients were alive. The data showed that a subgroup of subjects with low expression of HER2 had an ORR of 44.2%.[29]

Table 3. DESTINY trials

Name of Trial		
DESTINY-Breast01 phase II trial	Trastuzumab – deruxtecan (T-DXd, DS-8201) in unresectable/metastatic HER2-positive BC previously treated with at least two types of anti-HER2 agents.	HER2 + disease - response rate of 60.9% and a PFS of 16.4 months. Median duration of response = 20.8 months, estimated OS of 24.6 months.
DESTINY-Breast02 trial	Comparing T-DXd with the investigator's choice of treatment (trastuzumab + capecitabine or lapatinib + capecitabine) in confirmed HER2-+ unresectable and/or metastatic, progressing on/after T-DM1.	This DESTINY phase trial is ongoing.
DESTINY-Breast03, a phase III trial	Recruiting HER2 positive, unresectable and/or metastatic BC, initially treated with taxane-based chemotherapy and trastuzumab and will compare the efficacy and safety of T-DXd vs. T-DM1.	This DESTINY phase trial is ongoing.
DESTINY-Breast04	Assessing the efficacy of trastuzumab deruxtecan vs. investigator's choice (gemcitabine, eribulin, capecitabine, paclitaxel and nab-paclitaxel) in HER2-.	This DESTINY phase trial is ongoing.
DESTINY-Breast05	Comparing the two ADCs, T-DXd vs. T-DM1 in high-risk patients with HER2-positive, residual invasive early breast cancer after neoadjuvant therapy.	This DESTINY phase trial is ongoing.

The results presented in 2020 were also promising, showing a median duration of response (DOR) of 20.8 months and an estimated median OS of 24.6 months (95% CI, 23.1–NE).[30] There are other DESTINY phase trials, which are ongoing. The DESTINY-Breast02 is comparing T-DXd with the investigator's choice of treatment (trastuzumab plus capecitabine or lapatinib plus capecitabine) in patients with confirmed HER2-positive unresectable and/or metastatic BC that progressed on or after T-DM1. The DESTINY-Breast03, a phase III trial, is currently recruiting patients with HER2 positive, unresectable and/or/ metastatic BC which were initially treated with taxane-based chemotherapy and trastuzumab and will compare the efficacy and safety of T-DXd vs. T-DM1. DESTINY-Breast04 will assess the efficacy of trastuzumab deruxtecan vs. investigator's choice (gemcitabine, eribulin, capecitabine, paclitaxel *and nab*-paclitaxel) in HER2-low breast cancer.

DESTINY-Breast05 is comparing the two ADCs, T-DXd vs. T-DM1 in high-risk patients with HER2-positive, residual invasive early breast cancer after neoadjuvant therapy (Table 3).

The newly FDA approved monoclonal antibody, margetuximab, was studied in the SOPHIA trial, which compared margetuximab plus chemotherapy with trastuzumab plus chemotherapy in patients previously treated with minimum two anti-HER2 agents for metastatic BC. The end-points of the study were PFS, OS and safety, assessed by the incidence of grade 3 or higher adverse events. The results demonstrated that margetuximab plus chemotherapy reduced the risk of progression and death with 24% (HR, 0.76; 95% CI, 0.59-0.98; P=0.033) in a heavily pretreated population. The median PFS with margetuximab plus chemotherapy was 5.8 months compared with 4.9 months with trastuzumab plus chemotherapy. The experimental arm also demonstrated an improved median OS (22% vs. 16%).[31]

In real life practice, Trastuzumab plus Pertuzumab and chemotherapy are used for high-risk early breast cancer in the neoadjuvant and adjuvant setting and TDM1 in the adjuvant setting if patients

did not reach complete response after neoadjuvant trastuzumab plus chemotherapy. In the metastatic setting, the first line consists of trastuzumab and pertuzumab as standard of care with alternative TDM1, in the second-line (after Trastuzumab and Pertuzumab). In the third and later lines, we have options like Tucatinib, the latest FDA approved, in 17th Apr 2020, which has less activity on EGFR compared to Neratinib and Lapatinib, but with fewer side effects, Trastuzumab deruxtecan, that was FDA approved on 20th Dec 2019 based on the results of DESTINY Breast 01, despite the AE of the interstitial lung disease. Another later line option is Neratinib associated with capecitabine that received FDA approval on 25th Feb 2020, although with a great deal of digestive and skin toxicity. In these cases, it is necessary to correctly evaluate the co morbidities of the patients before starting the therapy.[32]

DISCUSSION

There are many new directions of research in HER2 positive BC: NRG B004: Atezolizumab added to Cleopatra regimen in the first-line metastatic setting, HER2CLIMB -02: TDM1 plus Tucatinib or placebo after trastuzumab/taxane+/-pertuzumab, TULIP: SYD985 (Duocarmacine derivate- antibody-drug conjugate) vs. trastuzumab or lapatinib with the physician's choice and the DESTINY-Breast 02, 03, 04. There are other antibody-drug conjugates in phase I studies: Monomethyl Auristatin (antitubulin), Amberstatin 269 (AS269) (antitubulin), Tubulysin (antitubulin).

The phase II double-blinded KATE2 trial randomized patients with advanced HER2 positive BC, who previously received treatment with trastuzumab and a taxane, into two arms: trastuzumab-emtansine plus atezolizumab and trastuzumab-emtansine plus placebo. Due to the increased number of patients on atezolizumab, who experienced side effects, the assigned arm was unmasked. The most common adverse effects (grade three or higher) were thrombocytopenia (13% patients on atezolizumab *vs.* 4% on placebo), increased AST and ALT values (5-8% *vs.* 3%), anemia (5% *vs.* 0) and neutropenia (5% *vs.* 4%). Serious adverse events were present in 33% of the patients who received atezolizumab vs. 19% of the patients who received Placebo and one patient on atezolizumab died due to hemophagocytic syndrome. The primary analysis (median follow up 8.5 months) showed a PFS of 8.2 months (CI 95%, 5.8-10.7) for the arm treated with atezolizumab and 6.8 months for the patients in the placebo arm (stratified hazard ratio 0·82, 95% CI 0·55–1·23; p=0·33). The addition of atezolizumab to T-DM1 did not significantly improve the PFS and was linked to increased adverse events. Further trials with atezolizumab in advanced HER2 + BC will include patients with PD-L1 positive tumors.[33]

Dual HER2-blockade in the neoadjuvant setting is the subject of numerous studies. Despite the inconsistency of the results, a meta-analysis conducted by Wang *et al*. suggests that neoadjuvancy with double blockade of HER2 plus chemotherapy improves the pCR rate in HER2+ BC. The meta-analysis included 11 studies and the subgroup analysis of combined-drug treatments revealed that combined regimens with lapatinib/pertuzumab increases the pCR rate by 28%, respectively by 37% in comparison with trastuzumab in monotherapy. Nevertheless, these results were not statistically significant and additional studies are necessary. The HR status can be a significant factor in the response rate to HER2 blockade. The percentage of HR+ tumors was variable in different trials, which can be the source of the inconsistency in the results.[34] Moreover, several studies demonstrated intratumoral heterogeneity, leading to the alteration of the efficacy of anti-HER2 agents.[35] These studies are crucial for the outcome of the patient. The use of neoadjuvancy in HER2+ positive disease has made possible conservative surgery without interference with prognosis and, very importantly, it improves the patient's psychological status. Moreover, numerous cases of pCR demonstrate that neoadjuvancy with HER2 blockade is the future standard in HER2 + BC.

The treatment of HER2+ ABC has experienced some changes in the last few years. In 2018, progression under first-line treatment with taxane-trastuzumab/pertuzumab and second line with T-DM1 was a big challenge, and was up to the oncologist to choose from lapatinib-capecitabine, trastuzumab-lapatinib, -capecitabine, -vinorelbine, -gemcitabine, -platinum or eribulin, depending on toxicities and therapies available in the country. However, nowadays we have a new third and fourth line FDA approved standard, which consists of tucatinib-trastuzumab-capecitabine and trastuzumab-deruxtecan. The fifth line relies on the oncologist's choice and consists of trastuzumab-chemotherapy, the benefit of neratinib-capecitabine being uncertain.

Regardless of the choice, Laakmann *et al*. demonstrated that the continuation of HER2 blockade after TDM1 in patients that have also been treated with pertuzumab offers a clinical benefit. The latest clinical trials that studied resistance mechanisms to anti-HER2 therapies have revealed positive prognostic improvements, suggesting the necessity of additional trials in patients who have a high probability of benefitting from further anti-HER2 treatments.[36]

CONCLUSION

The treatment of HER2+ disease is becoming more and more efficient. Over the years, clinical trials have showed great improvements in PFS, OS and pCR. Even though there are many challenges that we need to overcome, we are getting closer to an optimal version of treatment for HER+ BC by introducing new drugs and new indications for old drugs.

ETHICAL CONSIDERATIONS

This article does not contain any studies with human participants performed by any of the authors.

CONFLICTS OF INTEREST

The authors have no financial or non-financial interests to disclose.

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