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# Current challenges and unmet needs in treating patients with human epidermal growth factor receptor 2-positive advanced breast cancer

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ABSTRACT

Human epidermal growth factor receptor 2 oncogene (HER2-positive) overexpression/amplification occurs in less than 20% of breast cancers and has traditionally been associated with poor prognosis. Development of therapies that target HER2 has significantly improved outcomes for patients with HER2-positive advanced breast cancer (ABC). Currently available HER2-targeted agents include the monoclonal antibodies trastuzumab, pertuzumab, and margetuximab, the small-molecule inhibitors lapatinib, tucatinib, neratinib, and pyrotinib, as well as the antibody-drug conjugates trastuzumab emtansine and trastuzumab deruxtecan. Optimal sequencing of these agents in the continuum of the disease is critical to maximize treatment outcomes. The large body of clinical evidence generated over the past 2 decades aids clinicians in treatment decision-making. However, patients with HER2-positive ABC and specific disease characteristics and/or comorbidities, such as leptomeningeal disease, brain metastases, or cardiac dysfunction, are generally excluded from large randomized clinical trials, and elderly or frail patients are often underrepresented. In addition, there is great inequality in the accessibility of approved drugs across countries. This article addresses various challenging clinical situations when treating patients with HER2-positive ABC. The objective is to provide guidance to clinicians on how and when HER2-targeted therapies and additional treatments can be best implemented in routine clinical practice, on the basis of existing clinical evidence and expert opinion where needed.

## Purpose of this paper

The paper has the aim of providing support for clinical decision making in patients who do not meet the eligibility criteria from the pivotal trials which have led to the registration of the discussed drugs and is a complement to existing guidelines. This required review of cohort studies of "non-trial" patients receiving such treatments including important populations such as older patients and patients with brain metastases.

## 1. Introduction

Breast cancer is one of the most prevalent types of cancer worldwide,

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**Abbreviations**

| | |
|---|---|
| adj | adjuvant |
| Anthr | anthracycline |
| Cap | capecitabine |
| carbo | carboplatin |
| D | docetaxel |
| d | day |
| dox | doxorubicin |
| ERBB | erythroblastic leukemia viral oncogene homolog |
| HT | hormonal therapy |
| L | lapatinib |
| M | margetuximab |
| MCBS | magnitude of clinical benefit scale |
| med | median |
| N | neratinib |
| neo | neoadjuvant |
| PL | paclitaxel |
| PN | peripheral neuropathy |
| T | trastuzumab |

representing 11.7% of all new cancer cases in 2020, and responsible for 6.9% of cancer-related deaths [1]. In Europe, with a total of 84,900 predicted deaths for 2021, the breast-cancer age-standardized mortality rate was expected to decline by 7.8% in 2021 compared with 2015 [2]; however, the effects of the COVID-19 pandemic on health care may have influenced patients' survival [3,4].

Human epidermal growth factor receptor 2 overexpression or amplification of the *HER2/neu* oncogene (HER2-positive) occurs with variable incidence. For example, in the US, approximately 19% of patients under 50 years of age and 15% of patients aged 50 and older have HER2-positive breast cancer [5]. Among patients with early HER2-positive breast cancer, 16%–24% will progress and develop metastatic disease, with the major sites of distant metastasis being bone, liver, lung, and brain [6,7]; approximately 50% of patients with advanced breast cancer (ABC) develop brain metastases [8].

HER2-targeted therapies have significantly improved disease prognosis [9–12], with median overall survival (OS) longer than 60 months in patients with inoperable and previously untreated ABC [13]. HER2 expression, assessed at diagnosis and progression by immunohistochemistry and/or in situ hybridization (for detection of *HER2/neu* copy number) can predict potential responsiveness to HER2-targeted agents [14,15]. The quality of the samples used is key for accurate HER2 testing, and additional factors, such as intratumoral heterogeneity or changes in HER2 status at progression, can confound the interpretation of HER2 test results [16]. A review dedicated to the treatment of patients with HER2-low tumors has recently been published and will not be discussed in this article [17].

Multiple agents that target HER2 have been developed over the past decades (Table 1). Trastuzumab, the first anti-HER2 humanized monoclonal antibody, is key for treatment of HER2-positive breast cancer and has been included in the World Health Organization (WHO) Global Action Plan for Noncommunicable Diseases List of Essential Medicines [18]. The use of trastuzumab significantly improved disease-free survival and OS among patients with HER2-positive ABC [9,19]. A second anti-HER2 monoclonal antibody, pertuzumab, binds to different HER2 epitopes, making these agents complementary by providing increased HER2 blockade [20,21]. Consequently, dual HER2 targeting with trastuzumab and pertuzumab is the current standard of care for first-line ABC. However, pertuzumab is not available in routine practice for most patients in many countries [22] and there is existing or emerging resistance to anti-HER2 agents. As a result, anthracyclines, despite their cardiotoxicity and potential for development of secondary malignancies, are still used for many patients. The newest anti-HER2 monoclonal antibody, margetuximab, is engineered to induce CD16-mediated cytotoxicity and increase innate and adaptive immunity relative to trastuzumab and pertuzumab. Margetuximab has recently been approved by the US Food and Drug Administration (FDA) [23] on the basis of results from a phase III study showing marginally higher median progression-free survival (PFS; 5.8 vs 4.9 months) compared with trastuzumab, both plus chemotherapy, in pretreated patients with ABC [24]. Additionally, 2 antibody-drug conjugates (ADCs), trastuzumab emtansine (T-DM1), composed of the cytotoxic agent DM1 conjugated to trastuzumab [11], and trastuzumab-deruxtecan (T-DXd), which consists of trastuzumab and the topoisomerase I inhibitor DXd [25], are approved by the European Medicines Agency (EMA) and FDA. Finally, the HER2 tyrosine kinase inhibitors (TKIs) lapatinib and tucatinib (EMA-

**Table 1**
Targeted agents/regimens for HER2-positive locally advanced or metastatic breast cancer approved by EMA and/or FDA.

| Agent(s) | Mechanism of action | Mode of administration | Approved regimen |
|---|---|---|---|
| **Trastuzumab** | Anti-HER2 mAb | IV/SC | • Monotherapy after ≥2 CT regimens<br>• In combination with paclitaxel or docetaxel<br>• In combination with AI in HR-positive ABC |
| **Trastuzumab + Pertuzumab** | Anti-HER2 mAb | IV | • Trastuzumab + pertuzumab + docetaxel in 1L ABC |
| **Margetuximab-cmkb** | Anti-HER2 chimeric Fc-engineered mAb | IV | • Margetuximab + CT after ≥2 anti-HER2 regimens (at least 1 for ABC) |
| **Trastuzumab emtansine** | ADC (anti-HER2 mAb + DM1) | IV | • Monotherapy after taxanes + trastuzumab in 2L ABC or in 1L ABC for patients relapsing ≤6 m after adjuvant therapy |
| **Trastuzumab deruxtecan** | ADC (anti-HER2 mAb + DXd) | IV | • Monotherapy after ≥2 anti-HER2 regimens |
| **Lapatinib** | Reversible ERBB1 and ERBB2 TKI | PO | • In combination with capecitabine after 1L with anthracycline + taxanes + trastuzumab<br>• ≥2L: In combination with trastuzumab in HR-negative patients who progressed to CT + trastuzumab<br>• In combination with AI in patients with HR-positive ABC (patients did not previously receive AI or trastuzumab |
| **Neratinib** | Irreversible pan-ERBB TKI | PO | • In combination with capecitabine after ≥2 anti-HER2 regimens for ABC |
| **Tucatinib** | ERBB2 TKI | PO | • In combination with trastuzumab + capecitabine after ≥2 anti-HER2 regimens |

ABC, advanced breast cancer; ADC, antibody-drug conjugate; AI, aromatase inhibitor; CT, chemotherapy; EMA, European Medicines Agency; ERBB, erythroblastic leukemia viral oncogene homolog; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HT, hormonal therapy; IV, intravenous; L, line; mAb, monoclonal antibody; PO, oral; SC, subcutaneous; TKI, tyrosine kinase inhibitor.

and FDA-approved), neratinib (only FDA-approved for ABC) [26], and pyrotinib (approved in China only) have shown antitumor activity in patients with HER2-positive ABC [27,28]. Importantly, because of their low molecular weight, TKIs may pass through the blood-brain barrier and are potentially effective for patients with brain metastases [29]. Data from ongoing trials and approval of new drugs will further shape the treatment of patients with HER2-positive and HER2 low ABC.

The European School of Oncology (ESO)/European Society for Medical Oncology (ESMO) ABC5 guidelines for patients with HER2-positive ABC recommend the pertuzumab-trastuzumab and chemotherapy combination for patients who have not received previous HER2-targeted therapy or who were treated with a HER2-targeted agent in the (neo)adjuvant setting with a disease-free interval (DFI) over 12 months [30]. For second-line therapy, T-DM1 previously was the preferred option for patients who have progressed after at least 1 previous trastuzumab ± pertuzumab-based treatment. However, preliminary results from the DESTINY-Breast03 phase III trial in patients previously treated with trastuzumab and a taxane, where approximately half of the patients received T-DXd as second-line treatment and the other half in later lines [31], are reshaping the standard sequence of anti-HER2–targeted agents. Patients in the T-DXd cohort had a substantial PFS benefit compared with those receiving T-DM1 (hazard ratio = 0.28; $P = 7.8 \times 10^{-22}$; median PFS, not reached vs 6.8 months) and a trend toward an OS benefit (hazard ratio = 0.56; $P = 0.0072$ did not cross the preset boundary for significance of 0.000265). On the basis of these new data, the ABC6 guidelines [32] now state that, where approved, T-DXd is the preferred treatment option in the second-line setting, after pertuzumab-trastuzumab, and T-DM1 remains as first choice where T-DXd is not available or when patients cannot tolerate T-DXd. For patients who have been pretreated with pertuzumab-trastuzumab and T-DM1, treatment with T-DXd as monotherapy [31,33] or tucatinib in combination with trastuzumab and capecitabine have to be considered [34] according to their FDA- or EMA-approved indications [35–38]. Recent recommendations from the ABC6 [32] panel note that, if not used in the second line, T-DXd is the preferred treatment option in later lines of therapy, on the basis of its antitumor activity in heavily pretreated patients (median lines of previous therapy: 6) [33]. Dual blockade with tucatinib and trastuzumab in combination with capecitabine has shown a 2-month increase in median PFS and a 4-month increase in median OS compared with trastuzumab and capecitabine alone in patients previously treated with trastuzumab, pertuzumab, and T-DM1, including those with brain metastases [34,39]. Besides T-DXd and tucatinib, there is low-level evidence for any specific treatment option after second line and patients are encouraged to enroll in clinical trials, when available. Trastuzumab plus lapatinib or combinations of these drugs with chemotherapy or endocrine therapy (ET) may also be an option [40,41]. The main pivotal trials with approved HER2-targeted agents are represented in the Fig. 1 [9–11,19,20,24,33,34,42–54] and key results are summarized in Table 2 [9–11,19,20,24,31,33,34,42–57].

Novel drugs are evaluated in clinical trials, which enroll homogeneous patient populations and are strictly controlled under conditions that do not always reflect daily clinical practice. In general, patients with specific disease characteristics or comorbidities are excluded from clinical trials. Moreover, because of the lag period from drug approval to their inclusion in the guidelines and uptake by clinicians, patients' treatment history in daily practice does not always match that of the populations in pivotal studies. As a result, there are several clinical situations not covered by current evidence-based clinical practice guidelines (eg, elderly patients), which creates differences and misconceptions in clinical practice. Furthermore, unavailability of several HER2-targeted drugs in many countries contributes to treatment inequality and leads to unacceptable differences in clinical outcomes among patients worldwide. Herein, we discuss and provide expert recommendations for treatment in real-world patients with HER2-positive ABC for whom there are no specific clinical practice guidelines.

## 2. Methods

The focus of the manuscript, the selection of topics, and clinical scenarios for discussion were agreed by the co-authors during 5 online meetings. The topics were chosen on the basis of an author consensus, deleting many topics for which there was even less information.

The relevant literature was selected on the basis of the ESO/ESMO ABC5 guidelines [30] and authors' records (see Fig. 1). Searches of recent literature with keywords pertinent to the topics to be discussed were performed with a focus on HER2-positive ABC in PubMed and EMBASE databases (January 2020 through October 2021), including full manuscripts and congress abstracts. This search was performed for the authors and collection, analysis, and interpretation of data was done by the authors.

Authors' input on the existing evidence and their personal experience in the management of the defined clinical scenarios were collected and discussed during the meetings. All data and opinions were consolidated in a single draft, which was discussed until approved by all authors in its final version.

Access to specific treatments at the readers' respective country must be considered, and readers should adapt the recommendations accordingly.

## 3. Clinical scenarios

The treatment options for patients with HER2-positive ABC in the following specific clinical situations are discussed:

1. Resistance/progression to HER2-targeted therapies

Q1: For patients whose disease progresses during HER2-targeted maintenance therapy – should the last chemotherapy be resumed? (Per ABC guidelines, maintenance is defined as "the continuation of anti-HER2 therapy after discontinuation of chemotherapy" [30].)

- Available data: Evidence in support of rechallenge with the last chemotherapy is scarce and comes from a case series of 4 patients receiving pertuzumab-trastuzumab and docetaxel whose disease had progressed while on maintenance with pertuzumab-trastuzumab. Following rechallenge with paclitaxel, in 3 patients complete tumor response was achieved [58]. Following T-DM1 discontinuation, treatment with chemotherapy plus trastuzumab ± pertuzumab has shown limited antitumor activity [59]. Other options are reintroducing standard chemotherapy in combination with anti-HER2 treatment with trastuzumab-lapatinib [48] and pertuzumab-trastuzumab if patients have not previously been exposed to pertuzumab [46].
- ***Expert opinion***: Experts do not recommend the use of the previous chemotherapy for patients who had a short DFI (<12 months) after the last therapy. After progression to trastuzumab ± pertuzumab plus chemotherapy, switching to treatment with T-DM1, T-DXd, or tucatinib is advised and rechallenging should be considered only if there is no other option. Because the total duration of disease control comes from the added benefit of sequential treatments, the maximum potential from each line should be exhausted before switching to the next. Trials to address this question are needed.

Q2: For patients whose disease progresses under dual HER2 blockade – is rechallenging or continuing HER2 blockade beyond progression still a valid option?

- Evidence: HER2 expression levels play a role in the binding of anti-HER2 agents to cancer cells, limiting their antitumor activity. A preclinical study in HER2-positive breast cancer cell lines and in tumor biopsies from 4 patients treated with pertuzumab-trastuzumab has suggested that pertuzumab-trastuzumab

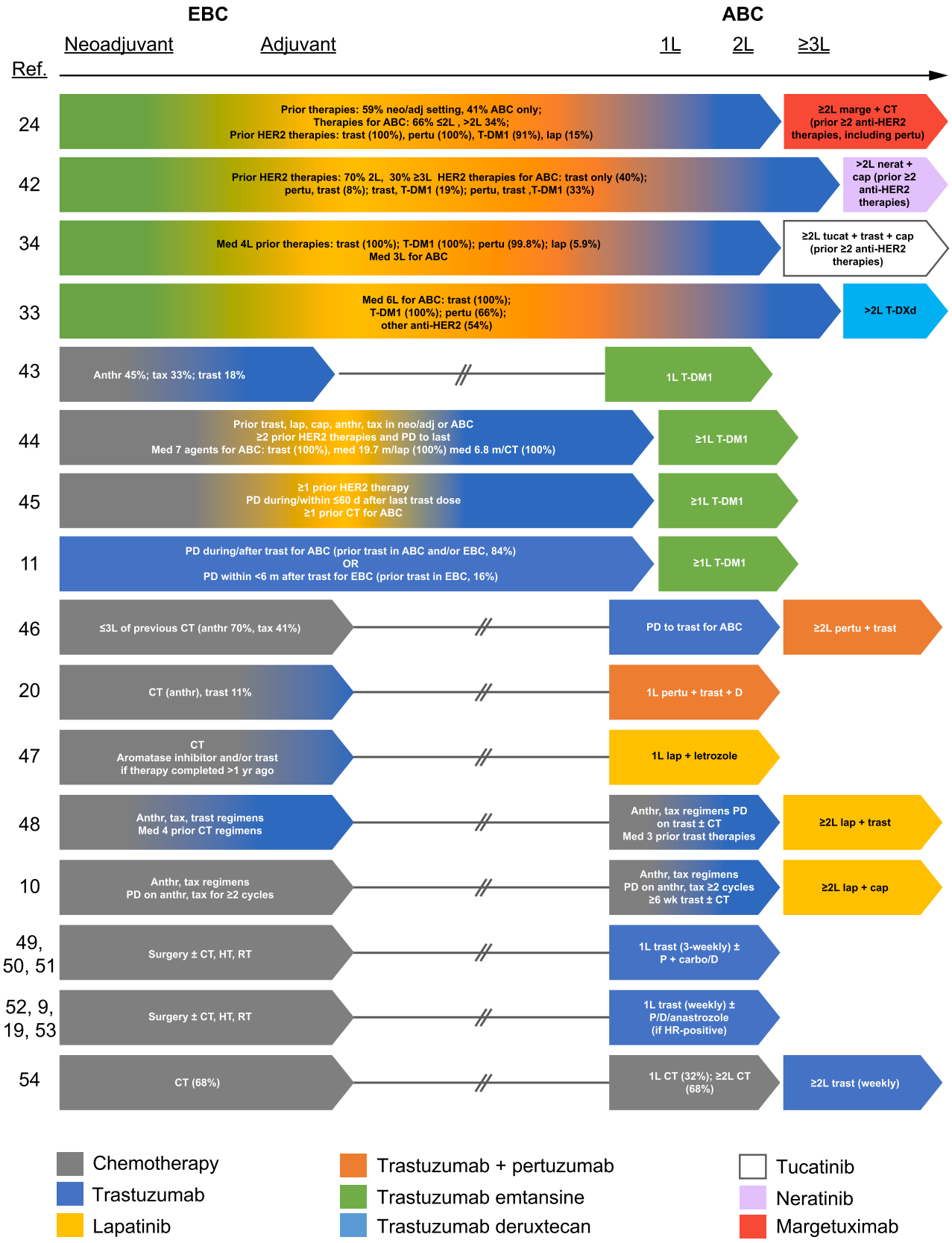


**Fig. 1.** Summary of trials of anti-HER2 agents approved by EMA and/or FDA for treatment of patients with locally advanced/metastatic breast cancer. We indicate the inclusion criteria to allow the reader to understand the typology of patients and the last arrow indicates the line of treatment of the actual trial. ABC, advanced breast cancer; adj, adjuvant; anthr, anthracycline; cap, capecitabine; carbo, carboplatin; CT, chemotherapy; D, docetaxel; d, day; EBC, early breast cancer; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HT, hormonal therapy; L, line; lap, lapatinib; marge, margetuximab; med, median; neo, neoadjuvant; nerat, neratinib; P, paclitaxel; PD, progressive disease; pertu, pertuzumab; RT, radiotherapy; tax, taxanes; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; trast, trastuzumab; tucat, tucatinib.

**Table 2**
Trials of targeted agents/regimens for HER2-positive locally advanced/metastatic breast cancer approved by EMA and/or FDA.

| Agent | | Trastuzumab | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Regimen | | Weekly | | | | | | Three-weekly | | |
| **Study** | | Cobleigh [54] (T) | Vogel [52] (T) | Slamon [9] (T + CT vs CT) | Slamon [9] (T + PL vs PL) | Marty [19] (T + D vs D) | Kaufman [53] (T + anastrozole vs anastrozole) | Baselga [49] (T) | Robert [50] (T + PL + carboplatin vs T + PL) | Herceptin SmPC [51] (T + D) |
| **N** | | 222 | 114 | 235 vs 234 | 92 vs 96 (68 vs 77*) | 92 vs 94 | 103 vs 104 | 105 | 98 vs 98 | 110 |
| **MCBS score** | | – | – | – | – | – | – | – | – | – |
| **Previous treatment** | **Neo/Adj** | • CT: 68% | • CT, 68%<br>• RT, 46%<br>• ET, 37%<br>• SCT, 12% | • CT: 72 vs 62%<br>• ET<br>• RT | • CT: 97 vs 100% | • CT, 71 vs 68%<br>• RT, 64 vs 66%<br>• ET, 44 vs 47% | • Adj/ABC CT ≥ 6 m prior, 53 vs 60%<br>• Adj/ABC ET, 60 vs 66% | • CT, 72%<br>• ET, 38%<br>• RT, 62% | • Surgery, 80 vs 76%<br>• CT: 49 vs 46%<br>• RT: 38 vs 42%<br>• ET: 40 vs 51% | – |
| | **ABC** | • CT ≥ 1L: 100% (1L, 32%; ≥2L, 68%) | • CT not allowed | • Adj/ABC ET: 58 vs 55%<br>• Adj/ABC RT: 55 vs 63% | • Adj/ABC ET: 55 vs 56%<br>• Adj/ABC RT: 67 vs 76% | • CT not allowed | | • CT, ET, RT not allowed | • CT not allowed | • CT not allowed |
| **Disease-free interval** | | • <12 m, 37%<br>• 12–24 m, 22%<br>• >24 m, 40% | • <12 m, 28%<br>• 12–24 m, 32%<br>• >24 m, 39% | • Med: 22.4–24.5 vs 18.9–22.8 m | • Med: 22.4 vs 18.9 m | – | – | – | – | – |
| **Patients excluded** | | • Bilateral BC<br>• Brain/only bone metastases | • Bilateral BC<br>• Brain/leptomenin-geal/only bone metastases | • Bilateral BC<br>• Brain/osteoblastic bone metastases | • Bilateral BC<br>• Brain/only bone metastases | • Brain/lepto-meningeal metastases<br>• LVEF <50%<br>• Uncontrolled cardiac disease | • Brain metastases<br>• LVEF <50%<br>• Uncontrolled cardiac disease | • Brain metastases<br>• LVEF <50%<br>• Uncontrolled cardiac disease | • Congestive heart failure<br>• Uncontrolled brain metastasis | • History of significant cardiac or CNS disorders<br>• LVEF <50% |
| **Efficacy** | | | | | | | | | | |
| ORR, % | | 15 | 26 | 50 vs 32 | 41 vs 17 (49 vs 17*) | 61 vs 34 | 20 vs 7 | 23 | 52 vs 36 | 73 |
| CR, % | | 4 | 6 | 8 vs 3 | 8 vs 2 | 7 vs 2 | 0 vs 0 | 2 | 10 vs 3 | – |
| Median TTP, m | | 3.1 | 3.5–3.8 | 7.4 vs 4.6 | 6.9 vs 3.0 (7.1 vs 3.0*) | 11.7 vs 6.1 | 4.8 vs 2.4 | 3.4 | – | 13.6 |
| Median OS, m | | 13 | 24.4 | 25.1 vs 20.3 | 22.1 vs 18.4 (24.8 vs 17.9*) | 31.2 vs 22.7 | 28.5 vs 23.9 | – | 35.7 vs 32.2 | 47.3 |

| Regimen | | Trastuzumab + pertuzumab | | Margetuximab | Trastuzumab emtansine (T-DM1) | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | | Baselga [20]; Swain [55] (P + T + D vs T + D) | Baselga [46] (P + T) | Rugo [24] (M + CT vs T + CT) | Verma [11] (T-DM1 vs L + Cap) | Hurvitz [43] (T-DM1 vs T + D) | Burris [45] (T-DM1) | Krop [44] (T-DM1) |
| **N** | | 402 vs 406 | 66 | 266 vs 270 | 495 vs 496 | 67 vs 70 | 112 | 110 |
| **MCBS score** | | 4 | – | – | 4 | – | – | – |
| **Previous treatment** | **Neo/Adj** | • CT ± T (TFI ≥12 m: 46 vs 47%) | • ≤3L of prior CT: Anthr, 70%; Tax, 41% tax | 59 vs 54% | • T: 16 vs 16% | • T: 18 vs 27%<br>• D: 33 vs 40%<br>• Anthr: 45 vs 49% | • ≥1L prior HER2 therapy<br>• Progressed while on HER2 therapy/≤60 d after last T dose | • T<br>• L<br>• Platinum<br>• Tax<br>• Anthr |
| | **ABC** | • ET in 1L | • Progressed to T | • ≤2L: 66 vs 67%<br>• >2L: 34 vs 33%<br>• Prior therapies in neo/adj or ABC: Tax, 95 vs 92%; Anthr, 44 vs 41%; Platinum, 13 vs 15%; T, 100 vs 100%; P, 100 vs 100%; T-DM1, 91 vs 92%; L, 15 vs 14%; ET, 47 vs 49% | • Progressed <6 m after neo/adj treatment or during/after prior ABC treatment<br>• T in neo/adj and/or ABC: 84 vs 84% | • CT not allowed | • ≥1L prior CT | • ≥2 L prior HER2 therapies and progressed to last<br>• Med 7 prior agents: T, 100%; L, 100%; Platinum, 100%; Anthr, 100%; Tax, 99%; RT, 86%; ET, 48% |
| **Disease-free interval** | | – | – | – | – | >24 m: 40 vs 36% | – | – |

(*continued on next page*)

**Table 2** (*continued*)

| Regimen | Trastuzumab + pertuzumab | | Margetuximab | Trastuzumab emtansine (T-DM1) | | | |
|---|---|---|---|---|---|---|---|
| **Patients excluded** | • Brain metastases<br>• Prior dox dose >360 mg/m2<br>• LVEF <50% | • Brain metastases<br>• Congestive heart failure<br>• LVEF <55% and if <50% during T | • Prior brain metastases were allowed if treated and stable | • Brain metastases<br>• Prior T-DM1, L, Cap<br>• PN G ≥ 3<br>• LVEF <50%<br>• Serious cardiac disease | • Progressed <6 m after neo/adj CT<br>• T ≤ 21 d prior<br>• Prior dox dose >500 mg/m2<br>• Brain metastases<br>• PN G ≥ 3<br>• Uncontrolled cardiovascular disease | • Brain metastases<br>• PN G ≥ 3<br>• LVEF <50%<br>• Serious cardiac disease | – |
| **Efficacy** | | | | | | | |
| ORR, % | 80 vs 69 | 24 | 22 vs 16 | 44 vs 31 | 64 vs 58 | 26 | 35 |
| CR, % | 6 vs 4 | 8 | 3 vs 2 | 4 vs 2 | 10 vs 4 | 0 | 0 |
| Median PFS, m | 18.7 vs 12.4 | 5.5 | 5.8 vs 4.9 | 9.6 vs 6.4 | 14.2 vs 9.2 | 4.6 | 6.9 |
| Median OS, m | 57.1 vs 40.8 (Prior T: 53.8 vs 46.6) | – | 21.6 vs 19.8 | 30.9 vs 25.1<br>29.9 vs 25.9† | – | – | – |

| Agent | Trastuzumab deruxtecan (T-DXd) | | Lapatinib | | | Tucatinib | Neratinib |
|---|---|---|---|---|---|---|---|
| **Study** | Modi [33] (T-DXd) | Cortes [31] (T-DXd vs T-DM1) | Geyer [10]; Cameron [57] (L + Cap vs Cap) | Blackwell [48,56] (L + T vs L) | Johnston [47] (L + letrozole vs letrozole; hormone receptor-positive, HER2-positive) | Murthy [34] (tucatinib + T + Cap vs T + Cap) | Saura [42] (N + Cap vs L + Cap) |
| **N** | 184 | 524 | 198 vs 201 | 148 vs 148 | 111 vs 108 | 410 vs 202 | 307 vs 314 |
| **MCBS score** | 2 | – | – | 4 | – | 3 | – |
| **Previous treatment** **Neo/Adj** | • Med 6 prior therapies: T, 100%; T-DM1, 100%; P, 66%; Other anti-HER2, 54% | – | – | – | • >1 yr prior: CT, ET, AI, and/or T | • Med prior therapies: 4 vs 4<br>• Med prior ABC therapies: 3 vs 3 | • Neo, 17 vs 23%<br>• Adj, 48 vs 48% |
| **ABC** | | | • T ± CT | • Med 3 prior T therapies | • None | • T, 100 vs 100%;<br>• P, 100 vs 100%;<br>• T-DM1, 100 vs 100%;<br>• L, 6 vs 5% | • Med 2L, 70 vs 69%<br>• Med ≥3L, 30 vs 32%<br>• T only: 40 vs 36%<br>• T, P + T: 8 vs 7%<br>• T, T-DM1: 19 vs 20%<br>• T, P + T, T-DM1: 33 vs 36% |
| **Disease-free interval** | – | – | – | 27 vs 25 d | – | – | – |
| **Patients excluded** | • History of cardiac disease | • Prior T-DM1 for ABC<br>• Uncontrolled/ significant cardiac disease<br>• Active brain metastases | • History of cardiac disease<br>• Abnormal LVEF<br>• Unstable brain metastases | • Abnormal LVEF | – | • Prior Cap or HER2 TKI for ABC (L allowed if > 12 m before)<br>• Leptomeningeal disease | • Prior brain metastases were allowed unless symptomatic or unstable |
| **Efficacy** | | | | | | | |
| ORR, % | 61 | 79 vs 34 | 22 vs 14 | 10 vs 7 | 28 vs 15 | 41 vs 23 | 33 vs 27 |
| CR, % | 6 | – | 1 vs 0 | 1 vs 2 | 5 vs 4 | 0.9 vs 1.2 | 1.6 vs 0.4 |
| Median PFS, m | 16.4 | Med 16 m follow-up: Not reached vs 6.8 | Med TTP: 8.4 vs 4.4 | 2.8 vs 1.9 | 8.2 vs 3 | 7.8 vs 5.6<br>At 1 yr:<br>33.1 vs 12.3% | 8.8 vs 6.6 |
| Median OS, m | At 12 m: 86.2% | At 12 m: 94.1 vs 85.9% | 17.3 vs 14.9 | 14 vs 9.5 | Med >7.5 yr follow-up: Hazard ratio 0.97; $P = 0.848$ | 21.9 vs 17.4<br>At 2 yr: 44.9 vs 26.6% | 24 vs 22.2 |

*Herceptin SmPC [51]. Subanalysis of patients with HER2 IHC3+ signal intensity.

†Long-term follow-up; 27.4% of patients had crossed from L + Cap to T-DM1 arm.

-, not specified; 1L, first-line; 2L, second-line; 3L, third-line; ABC, advanced breast cancer; adj, adjuvant; Anthr, anthracycline; BC, breast cancer; Cap, capecitabine; CNS, central nervous system; CR, complete response; CT, chemotherapy; D, docetaxel; dox, doxorubicin; EMA, European Medicines Agency; ET, endocrine therapy; FDA, Food and Drug Administration; G, grade; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; L, lapatinib; LVEF, left ventricular ejection fraction; M, margetuximab; m, months; MCBS, magnitude of clinical benefit scale; med, median; N, neratinib; neo, neoadjuvant; ORR, overall response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PL, paclitaxel; PN, peripheral neuropathy; RT, radiotherapy; SCT, stem cell transplantation; SmPC, summary of product characteristics; T, trastuzumab; T-DM1, trastuzumab emtansine; TFI, treatment-free interval; TKI, tyrosine kinase inhibitor; TTP, time to progression.

pretreatment can reduce the levels of HER2 receptors on cancer cells for subsequent T-DM1 targeting [60]. Additionally, T-DM1 efficacy has been suggested to be reduced in patients who received pertuzumab-trastuzumab in the previous line compared with those who received trastuzumab alone [61,62]. However, a phase III trial of pertuzumab retreatment (PRECIOUS; NCT02514681) has shown that pertuzumab-trastuzumab plus chemotherapy retreatment in third or fourth line is feasible [63]. Currently, switching to T-DXd is the preferred option for patients previously treated with trastuzumab plus taxane [31] and after T-DM1 [33]. Alternatively, retreatment with trastuzumab plus chemotherapy can be considered when T-DXd is not available [40,41,64].

– ***Expert opinion:*** It is crucial to keep blocking the HER2 pathway until the end of anticancer therapy, since progression of disease is much faster without blockade. If there is progression to dual blockade, rechallenge with the same agents is not recommended and other treatment options should be undertaken. Rechallenge may be considered if treatment was stopped for reasons other than progression, or if other therapy options have been exhausted or are not available. Maintained use of the HER2-targeted agent beyond progression (except trastuzumab [64]) is not recommended. Experts recommend use of other options before retreatment with pertuzumab.

Q3: For patients whose disease progresses under HER2-targeted therapy, is there a need to rebiopsy metastatic lesions?

– ***Expert opinion:*** After biopsy at presentation of ABC, rebiopsy may be performed at first progression or after "unexpected" evolution of the disease.

## 4. Third-line therapy and beyond

Q: For patients without brain metastases – what are the recommended third-line therapies?

– Evidence: T-DXd has recently been approved and has shown durable antitumor efficacy in heavily pretreated patients, including those who previously received T-DM1 [30,33]. Additionally, treatment with tucatinib in combination with trastuzumab and capecitabine has shown improvement in PFS and OS compared with trastuzumab plus capecitabine in heavily pretreated patients [34]. Other TKIs have also shown antitumor activity in patients with HER2-positive disease who had received various therapies in the metastatic setting. In retrospective analyses, lapatinib provided clinical benefit [65]; however, in phase III randomized clinical trials (NCIC CTG MA.31 [66,67] and CEREBEL [68] studies) combinations of chemotherapy and lapatinib were inferior to combinations of chemotherapy and trastuzumab in terms of OS. For this reason, the ABC guidelines consider the role of lapatinib as secondary and better used in combination with trastuzumab, without chemotherapy, in patients pretreated with several lines of therapy [48]. Notwithstanding the above, in countries without access to trastuzumab beyond progression, lapatinib remains a therapeutic option for patients who received prior trastuzumab, pertuzumab, and T-DM1. Additionally, neratinib provides a small improvement in PFS vs lapatinib (both in combination with capecitabine) in patients treated with $\geq$2 previous anti-HER2 therapies for ABC, but with the expenses of higher toxicity with diarrhea being the most relevant [42]. Marginal improvement in median PFS has been shown in a phase III trial of margetuximab vs trastuzumab (both in combination with chemotherapy [24]). Pyrotinib showed a benefit in median PFS vs lapatinib, both in combination with capecitabine [69]. Finally, preliminary results of an ongoing phase III trial with trastuzumab duocarmazine have shown slightly improved PFS in heavily pretreated patients (median 4 prior therapies for ABC) compared with physician's choice [70], but with important toxicity. Addition of everolimus to trastuzumab plus chemotherapy provides only minimal benefit in PFS [71], and is not recommended.

– ***Expert opinion:*** Upon progression while on second-line anti-HER2 therapy, treatment with TKI tucatinib, T-DM1 (if it was not used previously), and T-DXd should be considered, depending on availability and the risk-benefit ratio. The ABC6 guidelines do not recommend neratinib, pyrotinib, or margetuximab in this setting.

## 5. CNS metastases

Q1: For patients with progressive disease in the brain after double-blocking with pertuzumab-trastuzumab followed by T-DM1 – what are the treatment options?

– Evidence: The HER2CLIMB trial has shown that tucatinib added to trastuzumab plus capecitabine provides a survival advantage over trastuzumab plus capecitabine in patients with brain metastases and additional disease outside the brain [34]. A subgroup analysis in heavily pretreated patients with brain metastases enrolled in the HER2CLIMB trial showed that the tucatinib-trastuzumab-capecitabine combination was superior to trastuzumab-capecitabine in terms of PFS (68% reduction in the risk of progression or death) and OS (42% reduction in the risk of death) [39]. The phase II LANDSCAPE study showed that lapatinib plus capecitabine was active in patients with advanced disease and brain metastases not previously treated with radiotherapy [72]. The phase III randomized trial CEREBEL, of lapatinib plus capecitabine, was inferior in terms of OS to trastuzumab plus capecitabine and no difference was in seen in the primary endpoint of central nervous system (CNS) metastases [68]. Recently, T-DM1 [73,74] has shown some activity in patients pretreated with trastuzumab $\pm$ pertuzumab, while T-DXd has demonstrated preliminary activity in patients previously treated with T-DM1 [75,76]. For patients with stable systemic disease, the same systemic therapy is recommended (ABC6). When recurrence only involves brain metastases, following complete resection of 1–3 lesions, stereotactic radiotherapy (SRT) significantly reduced local recurrence compared with observation, with acceptable toxicity [77]. In a phase III study in patients with 1 resected brain metastasis, SRT showed similar OS and improved cognitive outcomes compared with whole brain RT (WBRT) and represented a less toxic option [78]. In patients eligible for SRT, addition of chemotherapy is not advised (ABC6).

– ***Expert opinion:*** The ABC6 recommendation for patients with progressive extracranial disease and without option for local therapy is to change the systemic therapy, with tucatinib plus trastuzumab and capecitabine being the preferred option (ABC6). Alternatively, patients can be treated with T-DM1, and preliminary evidence suggests that T-DXd can be used in patients pretreated with pertuzumab-trastuzumab and T-DM1 who had prior RT. For patients with controlled disease outside the brain, the advice is to treat the intracranial disease locally with surgery and/or SRT, when feasible, and to continue or resume treatment with the same HER2-targeted agent (ABC6). For patients with CNS progression after excision of brain metastases, the preferred option is local treatment, ie, surgery and/or SRT, when indicated. WBRT is an alternative with higher cognitive adverse events.

Q2: How has the use of SRT (eg, CyberKnife) changed the management of brain metastases?

– Evidence: WBRT has been the standard treatment for patients with brain metastasis, but its use has declined due to treatment-related toxicities, mostly cognitive impairment. Currently, WBRT use is mostly restricted to patients with numerous brain metastases and poor performance status. SRS, due to its highly conformal nature, spares a significant volume of healthy brain tissue and provides high

local control rates compared with WBRT. Two trials comparing SRS demonstrated no significant differences in OS and a lower risk of cognitive decline [79,80]. The risk of toxicity is related to the global volume, rather than the total number, of brain metastases. When compared with SRS alone, the addition of WBRT increases the risk of neurocognitive toxicity without conferring a benefit in OS.

- ***Expert opinion:*** In patients with up to 10 metastases and a volume of less than 30 $cm^2$, SRS is the recommended treatment option. Guidelines recommend against adjuvant WBRT following complete resection or SRS in favor of close monitoring for patients with a limited number of brain metastases.

Q3: For patients with leptomeningeal disease – what are the treatment options?

- Evidence: There is limited clinical evidence because this patient population is generally excluded from clinical trials, even from those enrolling patients with brain metastases. Results from 2 retrospective studies with low numbers of patients suggested that treatment with intrathecal trastuzumab [81] and intrathecal chemotherapy [82] might improve the prognosis of these patients. Treatment with T-DM1 and WBRT resulted in clinical and radiologic response in a single case-report [83]. While currently there are no data from clinical trials of TKIs in leptomeningeal disease, tucatinib in particular provides OS benefit for patients with brain metastases when in combination with trastuzumab and capecitabine [34,84]. An ongoing phase II study (NCT03501979) of the tucatinib-trastuzumab-capecitabine combination in patients with HER2-positive ABC and leptomeningeal disease should provide insight into the treatment options for this difficult-to-treat patient population.
- ***Expert opinion:*** Although there is no standard of care, ESO/ESMO ABC5 guideline recommendations include focal radiotherapy for patients with symptomatic lesions, WBRT for patients with extensive nodular or symptomatic disease, and intrathecal therapy for those with stable systemic disease and normal cerebrospinal fluid flow [30]. However, due to its toxicity and limited efficacy, intrathecal chemotherapy is rarely used. In general, the same treatments as for brain metastases discussed above could be used, despite the absence of direct evidence in patients with leptomeningeal disease [39]. Because of the small numbers of patients who develop leptomeningeal metastases, collection of real-world data would aid in the development of more specific and robust treatment recommendations. The prognosis of these patients remains dismal regardless of treatment.

## 6. Special populations

Q1: For frail patients, defined as patients with decreased physiologic and functional reserve resulting in increased predisposition to stressors and adverse outcomes, who are at risk of complications [85] – what are the treatment options? Is anti-HER2 therapy recommended?

- Evidence: Various HER2-targeted regimens without chemotherapy have shown antitumor activity and good tolerability, such as trastuzumab alone with addition of chemotherapy at disease progression [86], T-DM1 alone in first-line ABC [87], pertuzumab-trastuzumab followed by T-DM1 [88], or trastuzumab with lapatinib in heavily pretreated patients [48]. For elderly and frail patients, addition of metronomic cyclophosphamide to pertuzumab-trastuzumab led to benefits in PFS compared with the HER2 dual blockade alone, with an acceptable toxicity profile [89]. Additionally, for patients who cannot tolerate docetaxel or who have previously received docetaxel in the (neo)adjuvant setting, treatment with pertuzumab-trastuzumab and vinorelbine is a feasible option [90]. Lastly, treatment with trastuzumab plus ET was noninferior and was associated with fewer toxicities than trastuzumab plus chemotherapy in patients with HER2-positive, hormone receptor-positive ABC [91].
- ***Expert opinion:*** Chemotherapy should be omitted in these patients to reduce treatment-related toxicities, especially cardiotoxicity. HER2-targeted agents either as monotherapy or in various chemotherapy-free combinations are feasible options for frail patients. Alternatively, they can be combined with single-agent metronomic chemotherapy. For patients with hormone receptor-positive tumors, HER2-targeted agents in combination with ET should be considered.

Q2: For elderly fit patients – what are the treatment options? Is HER2-targeted therapy recommended?

- ***Expert opinion:*** Because fit elderly patients can tolerate standard treatment as younger patients do, age alone should not determine the choice of therapy [30,85]. Therefore, recommendations include the use of pertuzumab-trastuzumab plus a taxane (if the patient has adequate cardiac function) in first line, T-DXd in second line, and T-DM1 in later lines. Appropriate monitoring for occurrence of side effects (in particular diarrhea) associated with any type of regimen is strongly advised.

Q3: For patients with cardiac dysfunction – what are the treatment options?

- Evidence: Most pivotal trials exclude patients with cardiac dysfunction at baseline; thus, the cardiotoxicity of HER2-targeted agents may be underestimated. Among TKIs, tucatinib has not been associated with effects on left ventricular ejection fraction (LVEF) [34], while lapatinib and neratinib were reported to decrease LVEF in 2% and 4% of patients, respectively [42]. There is no evidence of increased long-term cytotoxicity following treatment with neratinib [92]. Anthracyclines are effective and used in breast cancer therapy despite their well-known cardiotoxicity [93], with liposomal formulations being associated with a much lower risk of cardiotoxicity than traditional anthracyclines. In patients with previously untreated ABC, liposomal doxorubicin monotherapy was well tolerated, with substantial antitumor effects [94].
- ***Expert opinion:*** Patients with severe cardiac dysfunction should in principle not be treated with anti-HER2 antibodies or ADCs, per the manufacturers' recommendations [35,36,51,95–99]. In cases of moderate cardiac dysfunction and metastatic disease with imminent risk of death, these agents may be considered with possibly simultaneous use of cardioprotective agents and with close monitoring by a cardiologist. TKIs can be used, since they have not been associated with cardiac toxicity if the manufacturers' instructions are followed. Finally, anthracyclines continue to play an important role, in particular for patients without access to anti-HER2 antibodies and TKIs.

## 7. Oligometastatic disease and low-burden disease highly sensitive to systemic therapy

Oligometastatic disease, according to the ABC guidelines [30], is defined as "low-volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status." A different clinical situation is low burden of disease highly sensitive to systemic therapy, as is the case of HER2-positive disease. These 2 clinical situations can be managed in a similar way, as discussed below.

Q: For patients with oligometastatic disease or low-burden disease highly sensitive to systemic therapy – should a multidisciplinary treatment approach with a curative intention be used?

- Evidence: Sporadic reports with low numbers of patients and patient cases from international registries have shown positive outcomes with surgery (complete resection of metastases [100,101]), radiotherapy (including stereotactic ablative body radiotherapy [102]), and systemic chemotherapy followed by surgery with or without radiation [103]. A small, randomized phase II trial enrolling patients with different types of cancers has shown substantial survival benefit when all metastases were treated locally [104]. However, more robust evidence from prospective randomized trials is needed.
- ***Expert opinion:*** In selected cases, for patients with oligometastatic disease or low-burden disease highly sensitive to systemic therapy who had a good response to systemic therapy, local therapy to the metastatic sites is an appropriate treatment option. The main treatment goal is to achieve long-term complete remission, which is associated with better survival [103].

## 8. Circulating tumor cells or DNA

Q: Does circulating tumor DNA (ctDNA) and circulating tumor cell evaluation have a role in treatment decision-making?

- Evidence: While available data are promising, the clinical applicability of these techniques is still experimental [105].
- ***Expert opinion:*** Their usefulness in individual decision-making is not established. However, ctDNA might be used to assess HER2 status in situations when expression cannot be detected with conventional methods or tumor material for repeat-biopsy is not available [106].

## 9. Conclusions/future perspectives

The prognosis of patients with HER2-positive ABC has improved dramatically since the introduction of HER2-targeted therapies. However, treatment of these patients remains an important medical challenge, as eventually most patients will progress while on treatment with approved HER2-targeted agents.

As a result of the fast development of this field, with constant approval of new drugs or new indications for the old ones, the treatment history of patients seen in daily practice usually does not correspond with that of patients who were enrolled in the registration trials. However, treatment paradigms, with HER2-targeted therapies as the backbone, are clear. When it is indicated and possible, upfront dual HER2 blockade is the standard. After progression, ADCs and TKIs may help overcome resistance to classical anti-HER2 monoclonal antibodies. Treatment selection will be guided by patients' comorbidities, disease presentation, and previous treatments and the toxicity profile of the drugs. Patients with specific disease characteristics and/or comorbidities (eg, leptomeningeal disease, cardiac dysfunction) are traditionally excluded from large randomized clinical trials, and particular populations, including elderly-frail and elderly-fit patients, are insufficiently represented in those trials. Consequently, the evidence of efficacy and safety with currently available HER2-targeted therapies in these populations is scarce, and real-world data are critical to aid in the treatment choice. In this article, we addressed some of the challenging situations when treating patients with HER2-positive ABC. The aim is to provide clinicians with treatment proposals that are based not only on clinical evidence but also on expert opinion, filling the gaps when evidence is not available.

With the expanded indication and use of available HER2-targeted therapies in the (neo)adjuvant setting, patients are already more heavily pretreated in the perioperative setting, making it a smaller but increasingly difficult-to-treat population when there is disease relapse.

New immunotherapies, such as anti-programmed death (PD)-1/PD-1 ligand 1 inhibitors and adoptive transfer of T cells expressing chimeric antigen receptors targeting HER2, as well as combinations of available anti-HER2 agents with cyclin-dependent kinase 4/6 inhibitors, and phosphoinositide-3 kinase inhibitors, are under investigation. How the new drugs will shape the landscape of HER2-positive ABC treatment and how they will fit in the sequencing of therapies remains to be seen.

Finally, progress in the management of HER2-positive ABC can only be accomplished if effective drugs are available to everyone. However, accessibility to essential drugs is not equal across countries, and it largely depends on the country's economic development [22], while inequalities within each country are also increasing. Trastuzumab, included in the WHO Model List of Essential Medicines for treatment of early and advanced breast cancer, is usually free (fully reimbursed) or available at reduced cost in high- and upper/middle-income countries, but only available at full cost for patients in lower/middle- or low-income countries [22]. Furthermore, even if available in some low- and middle-income countries, it is usually only for early breast cancer, and patients with advanced/metastatic disease do not have access to this essential medicine. The recent availability of trastuzumab biosimilars may improve global access to HER2-targeted therapy and reduce the inequality gap between countries [107]. Similarly, the availability of TKIs, pertuzumab, and T-DM1 differs substantially according to the economic level of the country [22]. New strategies are needed to ensure equal access of essential medicines and promote global equity in health care. Even the best drugs are only beneficial if they are accessible to patients. A full discussion of this important topic is unfortunately not possible in this paper.

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