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HER2-positive advanced breast cancer treatment in 2020

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ABSTRACT

HER2-positive breast cancer is an aggressive subtype identified in the 1980s. The development of therapies targeting the HER2 has improved outcomes. The current standard of care, established in 2012 is dual blockade with trastuzumab + pertuzumab as first-line followed by TDM-1 as second-line. Several suboptimal choices are available in third-line or more. In 2019 the presentation of several trials evaluating new drugs and regimens in third-line has re-opened questions about sequencing, treatment of triple positive disease and treatment choice after exposure to TDM-1. These include tucatinib, neratinib and trastuzumab-deruxtecan. Other agents – including other antibody drug conjugates and bispecific antibodies as well as combinations - will lead to further changes in coming years. Additionally, should the numerous putative biomarkers thus identified ever come into use at the clinic, choice of treatment and response evaluation may be substantially changed.

Introduction

Approximately 15–20% of breast cancers are human epidermal growth factor receptor-positive (HER2-positive), which is associated with worse survival outcomes as compared to estrogen receptor (ER) positive, HER2-negative breast cancer. Over the last 30 years, the development of a number of anti-HER2 agents improved outcomes in both early and advanced HER2-positive breast cancer [1]. Despite continuous efforts to develop innovative approaches and to improve patient care, management guidelines have nevertheless remained largely unchanged since 2012. Since 2019, however, a large number of trials were presented and 3 new drugs were approved, changing this situation.

This narrative review is focused on presenting current aspects of advanced HER2-positive breast cancer management, including current practices, new treatment options, and open research questions, with a particular focus on how to integrate trastuzumab-deruxtecan, tucatinib and neratinib into current guidelines based on the available evidence [2].

Current management of HER2-positive advanced breast cancer

Decision-making in HER2-positive advanced breast cancer depends essentially on 2 factors: (1) whether the patient has received trastuzumab previously; (2) time elapsed since the last dose of trastuzumab. This is a consequence of the inclusion criteria used in the CLEOPATRA and EMILIA trials [3–6]. It is important to highlight, however, that currently many patients diagnosed with advanced disease have been previously exposed to dual anti-HER2 blockade in the early settings based on data from the NeoSphere and APHINITY studies, among others [7–9]. Additionally, following KATHERINE study results, many patients receive T-DM1 in the early setting, further complicating decision-making. Table 1 summarizes the main findings of all pivotal trials for approved anti-HER2 agents in the advanced setting.

Briefly, "de novo" metastatic patients or those who develop metastatic disease after 6 months since the last dose of trastuzumab are candidates for first-line treatment with a taxane, trastuzumab and pertuzumab [5,10,11]. The results of the PERUSE clinical trial suggest that paclitaxel is no less effective than docetaxel, and that it may be less toxic. This has led geriatric oncologists to suggest that paclitaxel should be favored in older patients [12,13]. Patients who have progressed while on (neo)adjuvant trastuzumab or less than 6 months after its use or, alternatively, who progressed after receiving first-line with the CLEOPATRA regimen, should receive TDM-1 [6,14]. Patients who did not receive TDM-1 previously can receive it on subsequent lines [15,16]. Following the use of TDM-1, trastuzumab-based combinations with other cytotoxic agents or with lapatinib are common options, though sequencing and expected benefit remain unclear as these

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Table 1
Clinical practice determinant trials in advanced/metastatic HER2+ disease.

	Phase	Comparison	Scenario	Results		
				PFS	OS	RR
CLEOPATRA [5,10,11]	III	Docetaxel + H + Pert Docetaxel + H + Pla	1st line	18.7 m vs 12.4 m HR 0.68 (95%CI 0.58–0.80)	57.1 m vs 40.8 m HR 0.69 (95%CI 0.58–0.82)	80.2% vs 69.3%
EMILIA [6,14]	III	TDM-1 Cap + lapatinib	2nd line (100% previous H + taxane; no previous Pert)	9.6 m vs 6.4 m HR 0.65 (95%CI 0.55–0.77)	29.9 m vs 25.9 m HR 0.75 (95%CI 0.64–0.88)	46.3% vs 30.8%
DESTINY-Breast01 [23]	II	Single arm: Trastuzumab deruxtecan	> 2nd line (100% previous TDM-1; 65.8% previous Pert)	16.4 m	Median OS: NR 6 m-OS: 93.9% 12 m-OS: 86.2%	60.9%
HER2CLIMB [27]	III	Tucatinib + H + Cap Pla + H + Cap	> 2nd line (100% previous TDM-1 and H + Pert)	7.8 m vs 5.6 m HR 0.54 (95%CI 0.42–0.71)	21.9 m vs 17.4 m HR 0.66 (95%CI 0.50–0.88)	40.6% vs 22.8%
NALA [28]	III	Neratinib + Cap Lapatinib + Cap	> 2nd line (75% previous TDM-1; 42.5% previous H + Pert)	5.6 m vs 5.6 m HR 0.76 (95%CI 0.63–0.93)	21 m vs 18.7 m HR 0.88 (95%CI 0.72–1.07)	32.8% vs 26.7%
SOPHIA [29,30]	III	Margetuximab + chemo H + chemo	≥ 2nd line (90% previous TDM-1; 100% previous H + Pert)	5.8 m vs 4.9 m HR 0.76 (95%CI 0.59–0.98)	21.6 m vs 19.2 m HR 0.89 (95%CI 0.69–1.13)	25.2% vs 13.7%
TH3RESA [15,16]	III	TDM-1 Physician's choice	> 2nd line (100% previous H and lapatinib; no previous Pert)	6.2 m vs 3.3 m HR 0.53 (95%CI 0.42–0.66)	22.7 m vs 15.8 m HR 0.68 (95%CI 0.54–0.85)	31% vs 9%
EFG100151 [19,20]	III	Cap + lapatinib Cap	≥ 2nd line (97% previous H, taxane, and antracicline; no previous TDM-1 or Pert)	6.2 m vs 4.3 m HR 0.57 (95%CI 0.43–0.77)	18.7 m vs 16.2 m HR 0.87 (95%CI 0.70–1.08)	24% vs 14%
EGF104900 [17,18]	III	Lapatinib + H Lapatinib	≥ 2nd line (100% previous H; no previous TDM-1 or Pert)	2.8 m vs 2.0 m HR 0.74 (95%CI 0.58–0.94)	14 m vs 9.5 m HR 0.74 (95%CI 0.57–0.97)	10.3% vs 6.9%

PFS: median progression-free survival; OS: median overall survival; RR: objective response rate; H: trastuzumab; Pert: pertuzumab; Pla: placebo; m: months; Cap: capecitabine; TDM-1: trastuzumab-emtansine; chemo: chemotherapy.

regimens were developed before the use of pertuzumab and T-DM1 [17–22].

Open research questions in 2020

– *What should be the third-line and beyond approach for advanced HER2-positive breast cancer?*

There is no current recognized single standard third-line therapy option for HER2-positive advanced breast cancer [21,22]. Common options include trastuzumab + chemotherapy, trastuzumab + lapatinib and lapatinib + capecitabine. The combination of lapatinib + trastuzumab was compared with lapatinib alone in patients who had received a median of 3 previous trastuzumab-based lines. Results suggest a significant benefit with the combination in terms of progression-free survival (PFS) – 12 weeks vs 8.1 weeks, HR 0.73, 95% CI 0.57 to 0.93, p = 0.08. Overall survival (OS) was likewise improved – 14 vs 9.5 months, HR, 0.74; 95% CI, 0.57–0.97; p = 0.026 [17,18]. The lapatinib + capecitabine combination proved superior to capecitabine alone (PFS 8.4 months vs 4.4 months, HR 0.49, 95% CI 0.34–0.71, p < 0.001), with OS not being adequately evaluable due to crossover [19,20].

Trastuzumab-deruxtecan

Trastuzumab-deruxtecan (also known as DS-8201) is an antibody-drug conjugate that is composed of a humanized antibody targeting HER2 and a topoisomerase I inhibitor payload connected via a tetrapeptide-based cleavable linker. DESTINY-Breast01 was a single arm phase II trial, which tested the ideal dosage of this drug as well as its efficacy and safety. DS-8201 showed a response rate of 60.9% in heavily pre-treated HER2-positive population (with a median of 6 previous lines for metastatic disease) and a median PFS of 16.4 months. 86.2% of treated patients were alive at 12 months. It is important to highlight the occurrence of interstitial lung disease (ILD) in 13.6% of patients. Additionally, 2.2% of patients died due to treatment, 35.3% of patients required a delay in dosing, 23.4% a dose reduction and 15.2% discontinued treatment due to adverse events [23]. These results led to federal drug administration (FDA) approval of trastuzumab-deruxtecan in patients who received 2 or more lines of anti-HER2 therapy for advanced HER2-positive breast cancer. The phase III DESTINY-Breast02 confirmatory trial comparing trastuzumab-deruxtecan with capecitabine plus trastuzumab or lapatinib is ongoing (NCT03523585) .

ILD is the most clinically relevant emerging toxicity of trastuzumab-deruxtecan, as shown in an analysis of 7 trials with a total of 665 patients exposed to trastuzumab-deruxtecan. Sixty-six cases were reported (9.9%), with 13 being grade 3 or higher and 5 leading to death [24]. Other adverse events are also relevant when using trastuzumab-deruxtecan, including neutropenia, nausea and anaemia. It is important to note that, as with other agents which proved to have unexpected toxicities (such as trastuzumab with cardiac toxicity), rates and severity could diminish over time as patient selection and management improves.

Additional trials with DS-8201 include: (1) DESTINY-Breast03 which is comparing DS-8201 with TDM-1 in second-line (NCT03529110); (2) DESTINY-Breast04 which is testing DS-8201 in HER-low patients. Some lovel activity of trastuzumab-deruxtecan in HER2-low expressing tumors (2+ or 1+ and/or in situ hybridization negative), with a 44.2% response rate, was suggested in a phase I trial [25]. DESTINY-Breast04 is a phase III study comparing DS-8201 with physician's choice chemotherapy (capecitabine, eribulin, paclitaxel, nab-paclitaxel, gemcitabine) for HER2-low patients (NCT03734029). Should this study show an improvement in outcomes, treatment guidelines for tumours heretofore ideintified as luminal or triple negative will need to be adapted. Much remains to be done, however, to better understand HER2-low disease [26]. It is also important to note

that 2 phase 1 studies are exploring combinations of trastuzumab-deruxtecan with immunotherapy – durvalumab in NCT03523572 and pembrolizumab in NCT04042701.

Tucatinib

Tucatinib is an irreversible panHER tyrosine kinase inhibitor (TKI). Tucatinib in combination with trastuzumab and capecitabine improved median PFS (7.8 m vs 5.6 m; 33.1% vs 12.3% had not progressed at 1 year, HR 0.54, 95% CI, 0.42–0.71, p < 0.001) and median OS (21.9 m vs 17.4 m, 44.9% vs 26.6% alive at 2 years, HR 0.66; 95% CI, 0.50 to 0.88; P = 0.005) in comparison with trastuzumab, capecitabine and placebo in the phase III HER2CLIMB trial [27]. The triplet regimen reached a response rate of 40.6% in a population exposed to a median of three previous lines of treatment. The main toxicities observed were gastrointestinal (diarrhea), oral mucositis and hand-foot syndrome. Grade 3 or more events (55.2% vs 48.7%) and transaminases elevation were more frequent in the tucatinib arm. Tucatinib was discontinued more often than placebo (5.7% vs 3%) and capecitabine was discontinued more often in the tucatinib arm (9.8% vs 9.1%). Based on these results, FDA approval was granted in April 2020 for patients who received one or more previous lines of anti-HER2 therapy, including patients with brain metastasis. It is striking to note that the drug was approved for second-line though HER2CLIMB was conducted in third-line.

Neratinib

Neratinib + capecitabine improved PFS (5.6 m vs 5.5 m; HR 0.76, 95%CI 0.63–0.93) in comparison with lapatinib plus capecitabine in NALA trial. In a landmark analysis showed, PFS curves began to separate with 6-month PFS rates of 47% versus 38% and 1-year rates of 29% versus 15%. The coprimary endpoint of OS was not met (21 m vs 18.7 m; HR 0.88, 95%CI 0.72–1.07). There was 24% grade 3–4 diarrhea despite of mandatory loperamide use in the neratinib arm (vs 13% in the lapatinib arm). Overall, treatment discontinuation was more common in the lapatinib arm (14.5% vs 10.9%) [28]. It is noticeable however, that this worse tolerability of lapatinib could be due either to the lack of prophylactic loperamide or the higher dose of capecitabine use in the lapatinib arm. The FDA granted approval for the neratinib and capecitabine combination in March 2020 for patients previously exposed to at least 2 previous lines of anti-HER2 therapy.

Margetuximab

Margetuximab is an anti-HER2 antibody, with a Fc engineered domain designed for greater affinity to CD16A and reduced affinity to CD32B. The intended result is enhanced antibody dependent cellular cytotoxicity (ADCC) and thus superior anti-tumour effect as compared to trastuzumab. It is important to note that different alleles of CD16A impact on binding affinity, with the 158F allele determining reduced affinity and thus a weaker immune response under trastuzumab. In the SOPHIA trial, margetuximab associated with chemotherapy versus trastuzumab and chemotherapy in a population previously treated with standard first and second-lines, demonstrated a PFS improvement (5.8 m vs 4.9 m; HR 0.76, 95%CI 0.59–0.98), but no OS gain (21.6 m vs 19.2 m; HR 0.89, 95%CI 0.69–1.13). In a pre-specified subgroup analysis targeting patients with the CD16A 158F allele (86% of the sample), OS was 23.7 months in the margetuximab arm versus 19.4 months in the control arm (HR, 0.79; 95% CI, 0.61–1.04; p = 0.087). Margetuximab had more infusion-related reactions than trastuzumab (13.3% vs 3.4%), but only 1.5% were grade 3 or more [29,30]. FDA approval is pending.

In summary, there are 3 approved novel options for third-line therapy, all showing improvements in efficacy outcomes with different adverse event profiles and, critically, different control arms and populations, though it is important to keep in mind that the combination of trastuzumab, capecitabine and tucatinib is, at the moment, the only one to demonstrate an OS improvement in a population fully exposed to prior pertuzumab and TDM-1. In this respect, NALA results are the weakest with a high proportion of patients who did not receive pertuzumab and TDM-1 (Table 1).

Currently, therefore, available data does not allow definitive recommendations of one drug/regimen over another. When choosing third-line therapy, several questions should be considered: (1) treatment burden – with tucatinib and neratinib necessitating a large number of daily pills, (2) toxicity – risk of ILD vs impact of diarrhea and hand-foot syndrome on health and Quality of life (QoL), (3) brain disease, and the possibility of local therapy with surgery or radiotherapy.

It is the opinion of the authors of this manuscript that for most patients, trastuzumab-deruxtecan will be the treatment of choice in third-line, with tucatinib being used for patients with pre-existing lung illness or brain disease not amenable to local therapy in third-line or in fourth-line after trastuzumab-deruxtecan. The results of DESTINY-breast02 will shed further light on the issue. The issue of second-line tucatinib is more difficult – but it is reasonable to consider it an option over TDM-1 in patients in which brain disease is the most important clinical issue. It is important to stress however that no data on a head to head comparison between tucatinib and TDM-1 is available as well as no data on TDM-1 efficacy post-tucatinib exposure.

– *How should be managed patients progressing after receiving the KATHERINE regimen?*

No data is available today on how to proceed. It is reasonable to suggest that patients progressing during or early (within 12 months being an adequate yet empirical cut-off) after TDM-1 should probably be treated as third-line or treated with trastuzumab + pertuzumab (if they have not been exposed to pertuzumab in the early setting). Patients who progress later than 12 months remain an entirely open research question, with re-challenge, dual blockade or moving to further lines being entirely acceptable choices. In fact, there is no data supporting the lack of efficiency of trastuzumab-pertuzumab combinations after TDM-1.

– *How to choose systemic therapy in HER2-positive advanced breast cancer with brain metastasis?*

The incidence of brain metastasis is clinically significant in advanced HER2-positive breast cancer with approximately 50% of patients developing brain metastasis [31,32]. Median survival after brain metastasis is 25–27 months [33]. Local treatment with surgery and radiotherapy is the standard of care. Progressive CNS disease with controlled systemic disease is also a frequent scenario [34], and though little data is available, these patients receive local treatment and continue the same systemic regimen, whenever possible. It is important to note that pivotal studies such as DESTINY-breast02 do not discriminate between CNS and non-CNS progression and that therefore data coming from such studies will not help elucidate this clinically relevant question.

Though monoclonal antibodies, such as trastuzumab or TDM-1 have shown to have some activity in the CNS, TKIs are likely to have a superioir effect as they have a larger potential to penetrate the blood–brain barrier than antibodies and have demonstrated activity against CNS metastasis in a number of studies [35–40]. It is important to note, however, that lapatinib failed to prevent CNS relapses in CEREBEL [41].

HER2CLIMB included 45%-46% of patients with untreated brain metastasis. PFS in trastuzumab, capecitabine and tucatinib arm was superior to placebo for the subgroup with CNS disease (7.6 m vs 5.4 m; HR 0.48, 95%CI 0.34–0.69 and 1-year PFS 24.9% vs 0%). Furthermore, in the tucatinib arm, 40.6% of patients experienced an objective

response in the brain, vs 22.8% in the placebo arm ($p < 0.001$). These data match the previous 6.7 m PFS and 42% objective response for brain metastases with this triplet seen in a phase Ib trial [27,42]. An analysis focused on the subpopulation of patients with brain metastasis has further clarified the potential of tucatinib. In patients with previously untreated brain metastasis, median OS was 20.7 vs 11.6 months, HR 0.49, 95% CI 0.30-0.80, $p = 0.004$. Additionally patients with brain-only progression could receive local therapy and continue on study treatment. Time between first and second brain progression suggests that tucatinib could delay brain progression (median time to progression 7.6 vs 3.1 months, HR 0.33, 95% CI 0.13-0.85, $p = 0.02$) [93]

Neratinib likewise appears to reduce brain lesions, delay symptomatic progression of CNS metastasis and the need for intervention [28,43,44]. In the NEfERT-T study the risk of CNS progression was inferior in the neratinib arm (10.1% vs 20.2%; $p = 0.002$) [43]. In the NALA trial, neratinib was associated with fewer required interventions for brain metastasis (18% vs 24%) and with lower cumulative risk in time for these interventions (22.8% vs 29.2%; $p = 0.43$) [28]. The TBCRC022 trial was specifically designed to evaluate the effect of neratinib in CNS lesions. In a lapatinib-naïve population (cohort 3A) the response rate was 49% (all partial responses) and in a lapatinib-exposed (cohort 3B), 33%. Median PFS and OS for cohort 3A were 5.5 m and 13.3 m, respectively, and for cohort 3B were 3.1 m and 15.1 m [44]. When data for these three studies were combined, the occurrence of CNS response was associated with prolonged PFS (HR 0.58; 95%CI 0.31–1.10) and OS (HR 0.43, 95%CI 0.24–0.76) [45].

To conclude, treating patients with CNS disease remains a challenge. Though the data on tucatinib is provocative, foregoing local treatment for a systemic strategy upfront cannot be considered standard of care until a formal comparison of both strategies is made in a prospective trial. On the other hand, for patients who are not candidates for further local therapy, a TKI-based regimen is a reasonable approach rather than a monoclonal antibody-based approach. Tucatinib, the only drug tested in a triplet regimen and with evidence of OS benefit could be the best choice, though the lack of formal head to head comparisons of all three TKIs in equal circumstances is an important issue.

– *Should Triple Positive Disease be managed differently than ER-negative/HER2-positive disease?*

The management of HER2-positive/ER+ and HER2-positive/ER- is generally similar, with the inclusion of the triple positive subgroup in most trials evaluating HER2-target treatments. Older trials associating aromatase inhibitor (AI) and anti-HER2 agents demonstrated the superiority of the combination [46–48]. Current guidelines, however, do not suggest the use of first-line endocrine therapy with anti-HER2 therapy for all patients ER-positive patients. Three distinct roles are suggested in guidelines for endocrine therapy [21]:

(1) As first-line alone or in combination with anti-HER2 agents for selected patients considered not to be candidates for standard therapy for any reason – such patients with severe heart disease, extreme age and frailty;
(2) As “maintenance therapy” in addition to dual HER2 blockade with trastuzumab and pertuzumab in first-line, after the chemotherapy induction phase;
(3) In combination with trastuzumab or lapatinib in heavily pretreated patients or in patients deemed unfit for chemotherapy [4,22].

Recent years have seen a number of studies which contribute data to support this standard as well as suggesting a future path for more specific guidelines. These include the PERTAIN, ALTERNATIVE, PATRICIA and MonarcHER trials.

The PERTAIN trial, which included only triple positive tumours, randomized patients between an AI + trastuzumab or AI trastuzumab + pertuzumab. Patients could also receive induction docetaxel before initiating an AI (56% of patients did). Median PFS favoured the pertuzumab arm – 18.8 vs 15.8 months, HR 0.65; 95% CI, 0.48 to 0.89; $p = 0.0070$. Patients in the pertuzumab arm who did not receive induction had a median PFS of 21.7 months. Though this trial did not test “maintenance therapy” formally, patients in the pertuzumab arm had a similar PFS to those in CLEOPATRA (18.9 m and 18.8 m) [5,49]. The ongoing PATINA trial (NCT02947685) is evaluating the maintenance strategy by randomizing patients between AI and placebo, and will provide an answer to whether this strategy is valuable or not [3].

The ALTERNATIVE trial compared trastuzumab + AI with trastuzumab + lapatinib + AI and with lapatinib + AI in second-line setting. Prolonged PFS, response rate and a trend to improved OS were observed with the triplet regimen. Once more, no direct comparisons were done to confirm the benefit of endocrine therapy [50].

Cyclin D1 (CDK) 4/6 inhibitors, which have changed the treatment of advanced luminal tumours, have shown enhanced activity and have re-sensitized tumors to HER-target therapy in preclinical models, suggesting that it may be a pathway to resistance to anti-HER2 agents [51]. This rationale led to the development of phase II trials combining CDK 4/6 inhibitors and HER2 directed therapies in triple positive tumors.

The PATRICIA trial had the particularity of including patients with HER2-positive who were either ER-positive or negative. The ER + group was randomized to palbociclib + trastuzumab (Palb + T) with or without letrozole and the ER-, was treated with palbociclib + trastuzumab. In preliminary results at 6 months, 33.3% for patients in the ER- cohort, 40.0% in the ER + treated with Palb + T and 53.3% in the ER + treated with Palb + T + letrozole were free of disease progression. PAM50 was performed in order to ascertain outcomes by molecular subtype. Luminal subtypes were associated with superior PFS than other subtypes when exposed to trastuzumab + palboclib (12.4 m vs 4.1 m; HR 0.37, 95%CI 0.14–1.0) [52].

Finally, MonarcHER, included patients previously exposed to TDM-1 and comprised 3 arms: abemaciclib + trastuzumab + fulvestrant (A); abemaciclib + trastuzumab (B); trastuzumab + physician’s choice. Median PFS was longer in arm A than in arm C (8.3 m vs 5.7 m; HR 0.67, 95%CI 0.45–1.0; $p = 0.02$) and similar between arms B and C (5.7 m vs 5.7 m; HR 0.94, 95%CI 0.64–1.38; $p = 0.38$). The response rates were 35.4% (A), 16.5% (B) and 22.8% (C) and the safety profile was as expected for abemaciclib [53]. The apparent lack of benefit for abemaciclib in arm B is worthy of note, suggesting that either the improvement in outcomes seen in arm A is due to fulvestrant alone or that abemaciclib does not provide any benefit in the absence of a drug targeting the ER pathway.

To summarize, despite some new data, today current guidelines on the use of endocrine therapy and management of triple positive disease have not changed. Larger, better designed trials with CDK 4/6 inhibitors are needed before their benefit in HER2-positive disease can be strongly affirmed.

– *Are there any available biomarkers to guide choice of therapy today?*

In clinical practice, the use of anti-HER2 agents is based only in HER2 status which is the only predictive marker of response at this moment, without any substantial changes in the last 2 decades [54]. Data coming from clinical trials such as NeoSphere and PERNETTA, however, suggest that HER2-positive disease is a clinically heterogeneous disease, and that a portion of patients could be treated with de-escalated regimens containing anti-HER2 therapy alone. In PERNETTA, patients with advanced HER2-positive breast cancer were randomized between standard of care and dual blockade alone in first-line, with all patients receiving TDM-1 in first-line. Results show a significantly shorter PFS without chemotherapy, without any difference in OS. In the neoadjuvant NeoSphere trial, 17% of patients in the dual blockade without chemotherapy arm achieved a complete pathological response.

Identifying these patients who respond extremely well to anti-HER2 therapy alone and can be spared the toxicity of chemotherapy has been the focus of substantial translational research efforts, but today despite the identification of several biomarkers, no clinically validated strategy is available, and no treatment for HER2-positive disease is indicated on the basis of specific biomarkers [29,55,56].

In the future, this lack of biomarker-guided therapies may change, though not necessarily towards de-escalation. Clinically validating biomarkers is a long, difficult and expensive endeavor, and therefore it is more common for biomarkers to come into the clinic tied to the indication for new drugs rather than the suppression of older ones. Several examples of potential paths towards biomarker-based escalation are available, such as PIK3CA mutations and PI3K inhibitors, TiLs/PD-L1 and checkpoint inhibitors as well as CD16A-158 alleles and Mergetuximab (which has been previously described). In addition to these examples, liquid biopsy strategies and HER2-mutations are also being explored.

PIK3CA mutations Pi3K pathway inhibitors

Pi3K/Akt/mTOR pathway activation is one of the mechanisms of acquired resistance in HER2-positive tumors. Pi3K inhibitors are expected to overcome this resistance and to improve outcomes in previously refractory disease [57]. In the early setting complete pathological response (pCR) becomes less common after neoadjuvant chemotherapy when a PIK3CA mutation is present [58]. The troubled development of this class, with a high rate of adverse events seen in some trials, have delayed development in HER2-positive disease, but have however shown that outcomes are only improved in the presence of detectable PIK3CA mutations [59,60]

The largest presented study in HER2-positive disease, the neoadjuvant NeoPHOEBE trial was closed prematurely because due to limiting hepatic toxicity by buparlisib. Only 16% of the 50 patients recruited had a PIK3CA mutation, and no differences in response rates between buparlisib-trastuzumab and chemotherapy-trastuzumab were found [61].

There are ongoing phase I trials evaluating α-specific Pi3K inhibitors in HER2-positive cancers: taselisib associated with different anti-HER2 combination agents (NCT02390427); alpelisib + BYL719 (anti-HER3) + trastuzumab (NCT02167854); and alpelisip + TDM-1 (NCT02038010); MEN1611 + trastuzumab with or without fulvestrant (NCT03767335).

TiLs/PD-L1 immunotherapy agents

Several datasets point to TiLs impacting on outcomes in HER2-positive disease, and these have been recently reviewed by Soberino et al [62]. PD-L1 is the most commonly used biomarker to define the use of immunotherapy, though it is well understood to be suboptimal [63].

Check-point inhibitors have changed management in several solid tumours. In breast cancer, however, advance has been slower and is thus far limited in terms of approved regimens to triple negative breast cancer [64]. The significant prognostic and predictive value of TILs in HER2-positive breast cancer highlight its immunogenic nature. In HER2-positive advanced breast cancer, immunotherapy could be effective, based on pre-clinical models and some clinical data coming from early clinical studies [62].

PANACEA was the first trial combining anti-PD1 and anti-HER2 agents. This was a phase Ib/II single arm study of pembrolizumab and trastuzumab in a trastuzumab-resistant multi-treated population with 79.3% PDL-1 positivity. In PDL-positive patients, response rate was 15% and disease control rate was 25%. TiLs 5% or higher were significantly more common among patients who benefitted from treatment. There were no responses for PDL-1 negative cohort [65].

The phase II KATE2 study randomized patients previously treated with trastuzumab and a taxane to TDM-1 plus atezolizumab or placebo. Within a median follow-up of 18.2 m, the median OS was not reached yet. In the PDL-1 positive subgroup, the 1-year OS was superior for the atezolizumab arm (94.3% vs 57.9%), suggesting a possible OS benefit were these data became mature [66].

Other immunotherapy combinations are being evaluated in ongoing trials, such as trastuzumab, vinorelbine, avelumab with or without utomilumab in TDM-1 pre-treated patients (AVIATOR study: NCT03414658) and trastuzumab, pertuzumab and paclitaxel with or without atezolizumab in first-line therapy (NCT03199885).

Liquid biopsy

Circulating tumor DNA (ctDNA), commonly referred to as "liquid biopsy", promises to evaluate the amplification of HER2 in a reproducible and non-invasive way which would allow the dynamic monitoring of efficacy and treatment decision making [67,68]. A recent study verified the agreement of HER2 amplification in plasma ctDNA with primary tumor tissue, as well as the clinical significance of the change in HER2 copy number during anti-HER2 therapy. One of the cohorts had 26 metastatic patients whose HER2 status was positive in primary tissue. Their plasma copy numbers of HER2 were tracked in real time when receiving combined therapy with pyrotinib and capecitabine. In total, 19 out of 26 were identified as having HER2 amplification in ctDNA before the drug and the level of HER2 copy number in each patient decreased dramatically after 6 weeks of treatment targeting HER2. HER2 copy number did not fall below the amplification level in only two candidates, who experienced remarkably worse PFS (mean 3.2 months vs 21.9 months, $p < 0.001$). HER2 copy number also correlated with radiologic response to treatment. In some participants, the number of copies of HER2 increased for several weeks before the identification of progressive disease [69].

"Liquid biopsy" is not limited to ctDNA, and can mean evaluation of other potential markers, such as circulating tumour cells and circulating microRNA (ct-miRNA) had also been studied. Recently a study analyzed miRNA from 52 patients from NeoALTTO study [70]. Plasma samples were collected at baseline and 2 weeks after trastuzumab. RNA analysis identified two ct-miRNA (ct-miR-148a-3p and ct-miR-374a-5p) whose variation (increase) from baseline value were significantly associated with pathological complete response ($p = 0.008$ and 0.048, respectively), though, if the basal levels of either did not correlate with response.

To conclude, liquid biopsy techniques have potential, but are today to be considered strictly experimental in advanced breast cancer management.

HER2 mutations

Somatic HER2-mutations are a known mechanism of resistance to anti-HER2 treatment, which can impact the extracellular conformation of the receptor and hyper-activate the intracellular tyrosine kinase domain. In one metanalysis of 31 studies on the topic, with a total of 12,905 patients, the pooled incidence of mutations was 3.9%. 2 of these studies also reported on survival outcomes, suggesting that patients with mutations have worse prognosis [71]. Some pre-clinical as well as limited data coming from small studies suggest that TKIs such as poziotinib and neratinib can be effective in HER2 mutated tumours [72–74]. In one phase II study, 16 patients with HER2-mutated tumours received neratinib treatment. Outcomes suggest some effect, with a CBR of 31% and a median PFS of 16 [75].

– *What new drugs, classes or combinations are still in development?*

Many new agents, combinations and classes are in development currently, beyond those previously mentioned. Table 2 summarizes all ongoing studies.

Antibody-drug conjugates

Antibody-drug conjugates (ADC) combine the specificity of an antibody with the cytotoxic potential of chemotherapy agents [76]. Three ADCs are approved today for use in breast cancer, with 2 being

Table 2
Ongoing trials in HER2+ advanced breast cancer.

Drug	Trial/Drug sponsor	Phase	Population	Regimen	Sample size
Ipatasertib	NCT04253561 (Roche Pharma AG)	I	Advanced HER2+ PI3KCA-mutant breast cancer	Ipatasertib + trastuzumab + pertuzumab	25
TAEK-VAC-HerBy	NCT04246671 (Bavarian Nordic)	I/II	Advanced HER2+ cancer.	TAEK-VAC-HerBy	45
Pyrotinib	NCT04246502 (Chinese Academy of Medical Sciences)	II	HER2+ metastatic and have not received systemic anticancer therapy for advanced disease	Capecitabine + pyrotinib vs Capecitabine + trastuzumab + pertuzumab	200
	NCT04033172 (Chinese Academy of Medical Sciences)	II	HR+/HER2+ metastatic breast cancer	Pyrotinib + fulvestrant	40
	NCT04001621 (Jiangsu HengRui Medicine Co., Ltd.)	II	Trastuzumab-resistant HER2+ advanced breast cancer	Pyrotinib + capecitabine	100
	NCT03772353 (Jiangsu HengRui Medicine Co., Ltd.)	Ib/II	HR+/HER2+ relapsed/metastatic breast cancer	Letrozole + pyrotinib + DSHR6390	32
	NCT03997539 (Jiangsu HengRui Medicine Co., Ltd.)	II	HER2+ locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy	Pyrotinib + vinorelbine vs Treatment of physician's choice	265
	NCT03933982 (Chinese Academy of Medical Sciences)	II	HER2+ metastatic breast cancer with brain matastases	Pyrotinib + vinorelbine	30
Alpelisib	NCT04208178 (Novartis Pharmaceuticals)	III	HER2+ advanced breast cancer with PIK3CA mutation	Alpelisib + trastuzumab + pertuzumab vs Placebo + trastuzumab + pertuzumab	548
Poziotinib	NCT04172597 (Spectrum Pharmaceuticals, Inc.)	II	Advanced malignancies with EGFR or HER2 activating mutations	Poziotinib	150
	NCT02544997 (Samsung Medical Center)	II	Salvage treatment for metastatic BC with HER2 or EGFR mutation or activated AR or EGFR pathway	Poziotinib	30
GB221	NCT04164615/(Genor Biopharma Co., Ltd.)	III	Relapsed or metastatic patients who failed to respond to previous taxanes and/or anthracyclines	GB221 + capecitabine vs Placebo + capecitabine	336
	NCT04170595/(Genor Biopharma Co., Ltd.)	I/II	Metastatic BC who failed to respond to previous chemotherapy and no more than three lines and never received anti-HER2 treatment	GB221 1,2mg/Kg or 1,6mg/Kg or 1,8mg/Kg vs Trastuzumab vs GB221 + capecitabine vs Trastuzumab + capecitabine	132

(*continued on next page*)

Table 2 (*continued*)

Drug	Trial/Drug sponsor	Phase	Population	Regimen	Sample size
Palbociclib	NCT03709082 (Pfizer)	II	HR+/HER2+ metastatic breast cancer Prior treatment with a taxane and trastuzumab	Palbociclib + letrozole + TDM-1	4
	NCT02947685 (Pfizer)	III	After induction treatment for HR+/HER2+ metastatic breast cancer	Palbociclib + anti-HER2 therapy (trastuzumab/pertuzumab) + endocrine therapy vs Anti-HER2 therapy (trastuzumab/pertuzumab) + endocrine therapy	496
	NCT03530696 (Pfizer)	II	No > 2 lines of therapy for HER + metastatic breast cancer	TDM-1 + palbociclib vs TDM-1	132
	NCT04224272 (Zymeworks, Inc.)	II	Progressed or been refractory to prior treatment with trastuzumab, pertuzumab and TDM-1	ZW25 + palbociclib + fulvestrant	76
	NCT03304080 (Icahn School of Medicine at Mount Sinai)	I/II	No prior systemic treatment for metastatic breast cancer	Anastrozole + palbociclib + trastuzumab + pertuzumab	36
	NCT03913234 (Yonsei University)	I/II	Postmenopausal patients, without previous systemic therapy for advanced/metastatic breast cancer	Ribociclib + trastuzumab + letrozole	95
	NCT02448420 (SOLTI Breast Cancer Research Group)	II	HER2+ locally advanced or metastatic breast cancer who have received chemotherapy and trastuzumab in metastatic setting	Trastuzumab + palbociclib + endocrine therapy vs Physician's choice (TDM-1 or chemotherapy)	232
	NCT01976169 (Pfizer)	I	Recurrent or metastatic HER2+ breast cancer and RB-proficient	PD-0332991 + TDM-1	33
KN026	NCT03619681/(Jiangsu Alphamab Biopharmaceuticals Co., Ltd.)	I	Monotherapy in HER2+ advanced malignant breast or gastric cancer	KN026	20
	NCT04165993/(Jiangsu Alphamab Biopharmaceuticals Co., Ltd.)	II	HER2 expressing or positive metastatic breast cancer	KN026 combined with docetaxel vs KN026 monotherapy	70
A16	NCT03602079/(Klus Pharma Inc.)	II	Locally advanced/metastatic solid HER2+ tumors that did not respond or stopped responding to approved therapies	A166	82
Utomilumab	NCT03414658 (Pfizer)	II	Previous TDM-1 in any setting Previous trastuzumab and pertuzumab in the metastatic setting or within 12 months of neoadjuvant/adjuvant treatment	Trastuzumab + vinorelbine vs Trastuzumab + vinorelbine + avelumab vs Trastuzumab + vinorelbine + avelumab + utomilumab	100
	NCT03364348 (National Cancer Institute)	I	HER2-overexpressing breast cancer and radiographic evidence of metastatic or locally-recurrent unresectable disease	TDM-1 + utomilumab vs Trastuzumab + utomilumab	79
Neratinib	NCT03377387/(Puma Biotechnology, Inc.)	I/II	> 4 prior chemotherapy-based treatments in the metastatic setting are allowed. Previous TDM-1 Previous neratinib is not permitted. Previous capecitabine is allowed, if not combined with neratinib.	Capecitabine + neratinib	48
	NCT01494662/(Puma Biotechnology, Inc.)	II	HER2+ breast cancer with brain matastases	Neratinib vs Neratinib + craniotomy vs Neratinib + capecitabine (no prior lapatinib) vs Neratinib + capecitabine (with prior lapatinib) vs Neratinib + TDM-1 (previously untreated brain matastases) vs Neratinib + TDM-1 (progressive brain matastases) vs Neratinib + TDM-1 (progressive brain matastases and prior TDM-1)	168
	NCT03101748/(Puma Biotechnology, Inc.)	I/II	Primary metastatic or locally advanced breast cancer	Neratinib + paclitaxel + ertuzumab + trastuzumab vs Neratinib + paclitaxel + ertuzumab + trastuzumab + doxorubicin + cyclophosphamide vs Neratinib + paclitaxel + doxorubicin + cyclophosphamide	99
	NCT03289039/(Puma Biotechnology, Inc.)	II	Prior therapy with trastuzumab, pertuzumab or TDM-1 in any setting	Neratinib vs Neratinib + fulvestrant	

(*continued on next page*)

Table 2 (*continued*)

Drug	Trial/Drug sponsor	Phase	Population	Regimen	Sample size
Hemay022	NCT03308201/(Tianjin Hemay Pharmaceutical Co., Ltd.)	I	ER+/HER + breast cancer Post-menopausal females suitable for exemestane	Hemay022 + Exemestane	48
	NCT02476539/(Tianjin Hemay Pharmaceutical Co., Ltd.)	I	HER2+ advanced breast cancer	Hemay022	57
Eribulin	NCT03264547/(Eisai Co., Ltd.)	III	HER2+ advanced/recurrent cancer without prior chemotherapy agents	Trastuzumab + ertuzumab + taxane vs Trastuzumab + pertuzumab + eribulin	480
SYD985	NCT03262935/(Byondis B.V.)	III	Progression during or after at least two HER2-targeting regimens for locally advanced or metastatic disease or progression during or after TDM-1	SYD985 vs Physician's choice	345
TVB-2640	NCT03179904 (National Cancer Institute)	II	≤4 prior chemotherapy regimens in the metastatic setting	FASN inhibitor TVB-2640 + paclitaxel + trastuzumab	80
Atezolizumab	NCT03125928 (Genentech, Inc.)	II	HER2+ unresectable locally recurrent or metastatic breast cancer	Atezolizumab + paclitaxel + trastuzumab + pertuzumab	50
	NCT03417544 (Genentech, Inc.)	II	HER2+ with unequivocal evidence of new and/or progressive brain matastases	Atezolizumab + trastuzumab + pertuzumab	33
	NCT03199885 (National Cancer Institute)	III	HER2+ metastatic breast cancer	Pertuzumab + trastuzumab + paclitaxel + atezolizumab vs Pertuzumab + trastuzumab + paclitaxel + placebo	600
	NCT03650348 (Pieris Pharmaceuticals, Inc.)	I	HER2+ advanced or metastatic solid tumors	PRS-343 + atezolizumab	70
IFN-γ	NCT03112590 (Horizon Pharma Ireland, Ltd.)	I	HER2+ unresectable locally advanced or metastatic breast cancer	Interferon-γ + paclitaxel + trastuzumab + pertuzumab	43
RC48-ADC	NCT03052634 (RemeGen)	I/II	HER2+ locally advanced or metastatic breast cancer	RC48-ADC vs Lapatinib + capecitabine	165
	NCT03500380 (RemeGen)	II	HER2+ locally advanced or metastatic breast cancer	RC48-ADC vs Lapatinib + capecitabine	228
Olaparib	NCT03931551 (MedSIR)	II	HER2+ and gene alterations in HRR DNA pathway	Olaparib + trastuzumab	33

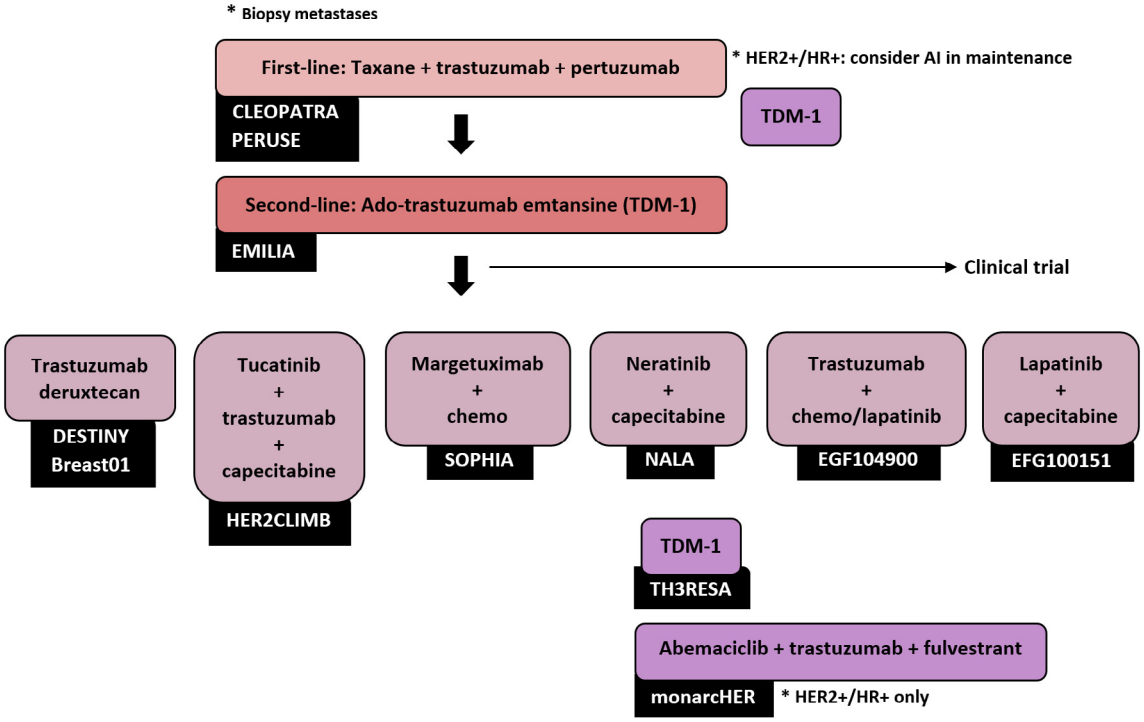

Fig. 1. Possible new treatment sequencing for HER2+ metastatic breast cancer.

specifically targeted against HER2 – TDM-1 and Trastuzumab-deruxtecan [77].

Other antibody-drug conjugates tested for HER2-positive metastatic breast cancer demonstrated clinical efficacy in phase I trials, including MEDI4276 (antibody conjugated to a microtubule inhibitor), RC48 (conjugated to a tubulin polymerization inhibitor, monomethyl auristatin E (MMAE)) and ARX88 [78–80]. Trastuzumab-duocarmazine (SYD985) was tested for both HER2-positive and HER2-low, heavily pretreated, tumors. Response rates were 36% and 60%,respectively, in the phase I trial [81]. In the expansion cohort, including 99 patients, the overall response rate for HER2-positive tumors was 33%, with a median PFS of 9.4 m. In the HER2-low population, it was 27% for hormone receptor positive and 40% for triple negative tumours [82]. An ongoing phase III (TULIP) trial comparing SYD985 with physician's choice in patients with HER2-positive metastatic tumors progressing after at least two previous anti-HER2 therapies, is currently recruiting (NCT 03262935).

Another approach, which is still in development, is to combine a monoclonal antibody to a payload agonist of myeloid cells, in order to drive a broad spectrum of anti-tumor immune response based on a potent activation of these cells. SBT6050 is an ADC composed by trastuzumab and TLR8 agonist. In preclinical models, it was associated with some efficacy in several tumor models as a single agent or in association with trastuzumab (the drugs bind to different epitopes, making this association feasible) [83].

Bispecific antibodies

Bispecific antibodies are antibodies capable of recognizing two different epitopes or antigens, blockading different pathways at the same time [84].

MCLA-128 is a bispecific humanized antibody targeting HER2 and HER3. Its efficacy in tumors NGR1 fusion-positive was demonstrated for lung, pancreas and other sites (basket design) in a clinical proof-of-concept clinical trial, and now a phase II study is ongoing [85]. In October 2019, an interim unplanned analysis of the phase II trial evaluating MCLA-128 in HER2-positive and HR+/HER2-low breast tumors was performed. The disease control and response rates were superior in the HER2-positive population, in which MCLA-128 was combined with trastuzumab and vinorelbine (75% disease control; 4% of confirmed responses and 17% unconfirmed in third line and beyond).

GBR 1302 targets HER2 and CD3 domains and was associated with stable disease (but no responses) in one early study. Infusion related reactions were the most common adverse effects and left ventricular ejection fraction decrease occurred in approximately 10% of the patients [86]. These data will probably encourage a phase II trial development.

ZW25 is a biparatopic anti-HER2 antibody, which binds two different epitopes in HER2 with preclinical evidence of potent inhibition of the pathway [87] which has shown some activity in various HER-positive tumours in phase 1. Two phase 1 trials are ongoing with this agent, one in pretreated HER2-positive tumours (NCT02892123) and one in triple positive-breast cancer in combination with fulvestrant and palbociclib (NCT04224272)

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors target the intracellular domains of receptors, thus bypassing extracellular domain conformational changes, which are a mechanism of resistance to monoclonal antibodies such as trastuzumab [88]. Anti-HER2 agents in this class include lapatinib, tucatinib and neratinib. 2 more agents, pyrotinib and poziotinib are in advanced stages of development.

Pyrotinib is an irreversible pan-HER inhibitor (targets HER1, HER2 and HER4) that showed 50% overall response rate and a median PFS of 35.4 weeks in a phase I trial [89]. A phase II Chinese trial published in 2019 compared the combination of pyrotinib or lapatinib and capecitabine for HER2-positive breast cancer with 2 prior lines for metastatic disease. Only 29.7% of the population had received prior anti-HER2 therapy for advanced tumors. Pyrotinib was associated with increased PFS (18.1 m vs 7.0 m; HR 0.36, 95%CI 0.23–0.58) and overall response rate (78.5% vs 57.1%; p = 0.01), with more grade 3–4 adverse events (diarrhea, hand-foot syndrome, vomiting and neutropenia without fever were predominant) [90]. These results have been confirmed in Considering the absence of HER2-target therapies in first and second-lines in most cases, this could not be considered a worldwide

representative population, and so, more studies are needed to evaluate the most appropriate scenario to use this drug outside of China.

Another irreversible pan-HER inhibitor, poziotinib, was initially evaluated in a phase I trial that included multiple types of metastatic tumors, with the majority being exposed to 4 or more lines of previous regimens. The overall response rate was 16% and 47% had stable disease. [74] The NOV120101-203 trial enrolled 106 patients with metastatic HER2-positive breast cancer and previous 2 anti-HER2 therapies to poziotinib monotherapy. This drug exhibited a 4.04 m a median of PFS and 25.5% response rate [91].

Conclusion

In 2019, important data on several options of third-line (and beyond) were presented leading to their rapid approval by the FDA, raising questions about the best choice of treatment to be adopted for advanced HER2-positive breast cancer in third-line (Fig. 1). The trials which led to approval are, however, vulnerable to criticism and their designs mean that currently there is little data to base decisions on. It is the opinion of the authors of this manuscript, however, that trastuzumab-deruxtecan will likely be the choice of third-line for most patients, with tucatinib being used for patients with severe lung comorbidities or CNS disease that is not amenable to local treatment. Sadly, despite substantial research efforts, no biomarkers are today available to base decision-making. Trials that integrate biomarkers into design are urgently needed.

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