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Anti-Tumour Treatment

Treatment of advanced HER2-positive breast cancer: 2018 and beyond

Noam Pondé[a,*], Mariana Brandão[b], Georges El-Hachem[c], Emilie Werbrouck[d], Martine Piccart[e]

[a] Academic Promoting Team, Institut Jules Bordet, Blvd de Waterloo 121, 7th Floor., 1000 Brussels, Belgium
[b] Academic Promoting Team, Institut Jules Bordet, Belgium
[c] Medical Department, Institut Jules Bordet, Belgium
[d] Medical Oncology Department, University Hospital Leuven, Belgium
[e] Research Department, Institut Jules Bordet, Belgium

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ABSTRACT

In the 1980s the importance of HER2 signalling to the aberrant behaviour of a subset of breast cancer cells was recognized for the first time and, consequently, a hitherto unknown subtype of breast cancer – HER2-positive (HER2+) breast cancer was identified. The development of the anti-HER2 class of drugs, first with trastuzumab, followed closely by lapatinib, pertuzumab, and T-DM1, has improved outcomes dramatically. Nevertheless, metastatic HER2+ breast cancer remains an incurable disease and new therapeutic options are needed. Additionally, the rapid changes in treatment standards 5 years ago have left unanswered numerous questions, including the "real-life" benefit of pertuzumab and T-DM1, since both the CLEOPATRA and EMILIA trials were conducted in populations that no longer exist in practice and, moreover, on the role of endocrine therapy in HER2+ disease. Furthermore, despite significant research efforts, including translational efforts and new imaging techniques, no predictive biomarkers have been clinically validated and therefore a more refined approach to treatment tailoring remains beyond our reach. Finally, a better understanding of resistance to currently existing anti-HER2 agents and of the role played by the microenvironment (e.g. immune system) and of interconnected signalling pathways (e.g. PI3K-mTOR-AKT) is at the core of clinical trials exploring new drugs and new regimens. These include the combination of anti-HER2 agents and anti-PD-1/PDL-1, PI3K inhibitors and CDK 4/6 inhibitors, as well as a host of new panHER inhibitors, drug antibody conjugates and anti-HER antibodies, which may, in coming years further push the boundaries of what we can do for our patients.

Introduction

The aberrant behaviour of cancer relies on the subversion of growth signalling receptors and pathways [1]. In breast cancer (BC), human epidermal growth factor receptor 2 (HER2) is especially relevant [2]. BC that overexpresses HER2 (HER2+) forms a subpopulation amounting to 15–20% of cases, with an aggressive clinical behaviour [3]. Intense research efforts have yielded, starting with trastuzumab, a class of anti-HER2 agents that includes today 4 approved agents in the advanced setting – trastuzumab, lapatinib, pertuzumab and T-DM1. These agents have doubled median overall survival (OS) – today surpassing 50 months, and more than tripled the 5-year survival rate [4]. A number of research questions, however, remain open on the best sequencing of available regimens, on how to treat estrogen receptor positive (ER+)/HER2+ disease, as well as on how to improve treatment tailoring for the individual patient.

This review will provide an updated look at all current aspects of the evolving field of advanced HER2+ BC (MBC), covering current management, open research questions, the state of predictive biomarker development, as well as ongoing drug development efforts aiming at further improving patient outcomes.

Current management of HER2+ advanced disease

According to international guidelines, patients with metastatic HER2-positive BC (MBC) should be stratified according to prior exposure to trastuzumab and time elapsed between last dose and disease relapse [5,6]. Table 1 summarizes the results of key trials determining current standards and Fig. 1 summarizes guideline recommendations.

Most patients should receive anti-HER2 therapy associated with chemotherapy [5,6]. Patients who have not been exposed to trastuzumab or who develop metastatic disease 6 months after adjuvant trastuzumab are candidates for first line treatment with a taxane, trastuzumab and pertuzumab [7,8]. However, if disease progression occurs while on trastuzumab or with a treatment free interval of less than 6 months, direct second line treatment with T-DM1 is likely the

* Corresponding author.
E-mail address: Noam.ponde@bordet.be (N. Pondé).

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Table 1
Results of key trials determining clinical practice in advanced/metastatic HER2+ disease.

Trial	ClinicalTrials.gov number	Nb. of patients	Line of treatment (advanced setting)	Treatment arms (control vs. experimental)	Results (control vs. experimental)	
					PFS	OS
CLEOPATRA	NCT00567190	808	1st line; TFI > 12 months	Docetaxel + Trastuzumab vs. Docetaxel + Trastuzumab + Pertuzumab	12.4 m vs. 18.7 m HR 0.68 (95% CI 0.58–0.80)	40.8 m vs. 56.5 m HR 0.68 (95% CI 0.56–0.84)
EMILIA	NCT00829166	991	2nd line (after progression on trastuzumab and taxane) or TFI < 6 months	Capecitabine + Lapatinib vs. T-DM1	6.4 m vs. 9.6 m HR 0.65 (95% CI 0.55–0.77)	25.9 m vs. 29.9 m HR 0.75 (95% CI 0.64–0.88)
TH3RESA	NCT01419197	602	≥2nd line (after progression on taxane, trastuzumab and lapatinib)	Treatment of physician's choice vs. T-DM1	3.3 m vs. 6.2 m HR 0.53 (95% CI 0.42–0.66)	15.8 m vs. 22.7 m HR 0.68 (95% CI 0.54–0.85)
Geyer et al.	NCT00078572	399	≥2nd line (after progression on trastuzumab, taxane and anthracycline)	Capecitabine vs. Capecitabine plus Lapatinib	4.3 m vs. 6.2 m HR 0.57 (95% CI 0.43–0.77)	15.3 m vs. 15.6 m HR 0.78 (95% CI 0.55–1.12)
EGF104900	NCT00320385	296	≥2nd line (after progression on trastuzumab)	Lapatinib vs. Lapatinib + Trastuzumab	8 weeks vs. 11 weeks HR 0.73 (95% CI 0.57–0.93)	10 vs. 14 months HR 0.75 (95% CI 0.53–1.07)

Abbreviations: m: months; OS: median overall survival; ORR: overall response ratio; PFS: median progression free survival; T-DM1: adotrastuzumab emtansine; TFI: trastuzumab-free interval (in the neoadjuvant or adjuvant setting).

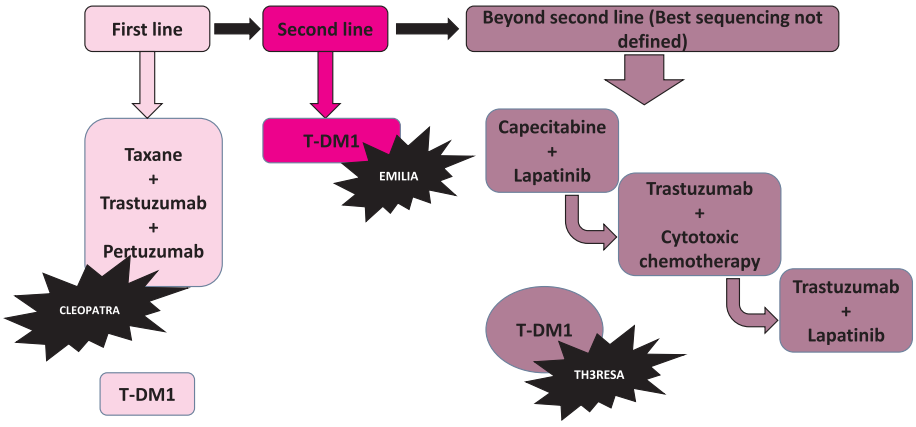

Fig. 1. Current advanced HER2-positive breast cancer treatment guidelines.

best option [9–11]. Patients who have received first line treatment as per the CLEOPATRA trial, are candidates for T-DM1 in second line [6]. Following the use of T-DM1, lapatinib containing combinations or chemotherapy + trastuzumab are standard options, though sequencing is not clear as these regimens were developed before the use of pertuzumab and T-DM1 [12–14]. Finally patients who do not receive T-DM1 in first or second line can receive it in third line or more [15,16].

Open research questions in 2018

What is the efficacy of pertuzumab in trastuzumab – pre-treated "real life" populations?

Only 23% of patients in CLEOPATRA received adjuvant trastuzumab, which is strikingly different from "real life" clinical practice [17]. These pre-treated patients had to have trastuzumab-free interval greater than 12 months in order to participate but, even so, presented worse PFS compared to trastuzumab-naïve patients, both in the pertuzumab-arm (16.9 vs. 21.6 months) and in the control-arm (10.4 vs. 12.6 months), when compared to patients with *de novo* disease. They seemed, nevertheless, to derive benefit from the dual blockade (median PFS of 16.9 vs. 10.4 months in the control arm). This difference in outcomes may be due to the development of trastuzumab-resistant disease, but the impact of resistance on the response to the combination of trastuzumab with pertuzumab is not fully understood.

Further data comes from the PHEREXA trial evaluating dual blockade with pertuzumab + trastuzumab + capecitabine for patients previously treated with a taxane and trastuzumab in the metastatic setting. Results show no improvement in median PFS with the addition of pertuzumab (11.1 vs. 9.0 months, HR 0.82; 95% CI 0.65–1.02) [18], but better median OS (36.1 vs. 28.1 months; HR 0.68, 95% CI 0.51–0.90). A similar trend towards diminished benefit in trastuzumab pre-treated patients comes from a preliminary analysis of the SUPER trial, which tested the CLEOPATRA regimen in 248 patients, 62.5% of which had received adjuvant trastuzumab (median PFS of 17.3 months for the trastuzumab naïve vs 14.9 months for the trastuzumab pre-treated) [19]. Additionally, a small case series with 35 patients treated with trastuzumab in the (neo)adjuvant setting and who received first-line therapy with trastuzumab + pertuzumab + docetaxel showed a median PFS of 12 months (95% CI 2–38), and a median OS of only 15.2 months (95% CI 2–36), which is strikingly lower than the 56.5 months observed in CLEOPATRA [20].

These few data suggest that the "real life" benefit from dual blockade in trastuzumab pre-treated patients is smaller than what was seen in CLEOPATRA. In the near future, the results of trials such as PERUSE (NCT01572038) as well as national registries such as SystHERs (NCT01615068), SAMANTHA (NCT02913456) and HER2-OBS are likely to resolve this question [21].