

Current Standards and Future Outlooks in Metastatic Her2-Positive Breast Cancer

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Keywords

Trastuzumab · Antibody-drug conjugates · Tyrosine kinase inhibitors · Brain metastases

Abstract

Background: Approximately 20% of all breast cancer cases show overexpression or amplification of the human epidermal growth factor receptor 2 (Her2) [Cancer Epidemiol Biomarkers Prev. 2017;26(4):632–41]. With the introduction of trastuzumab, lapatinib, and pertuzumab to the realm of treatment, a new era of antibody-drug conjugates had only begun. Within the last two decades, survival for patients with this tumor subtype has fundamentally improved. **Summary:** Beginning with a taxane plus trastuzumab/pertuzumab followed by trastuzumab deruxtecan, the first- and second-line treatments are set in stone. With the introduction of tucatinib as a newer tyrosine kinase inhibitor in combination with capecitabine and trastuzumab, there is one efficient line of treatment available after trastuzumab deruxtecan or even earlier in selected cases with active brain metastasis. Especially for later stages of disease, several combination strategies are under investigation. There is still a lack of positive results on immune checkpoint inhibition combined with Her2-targeted therapy, but hopefully an extension to the treatment algorithm will be on its way soon. **Key Messages:** With the HER2CLIMB trial, patients with brain metastasis were no longer excluded from bigger trials, and international guidelines implemented its presence or absence in their decision trees [N Engl J Med. 2020;382(7):597–609]. Curing Her2-positive metastatic breast cancer, or at least living a long life with this disease, is increasingly becoming a reality.

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Introduction

The amplification or overexpression of human epidermal growth factor receptor 2 (Her2) can be found in approximately 20% of all breast cancer cases [1]. Historically, this subtype was associated with more aggressive disease behavior and worse survival. However, due to the development of new Her2-targeted therapies such as monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADCs), there has been a huge change in disease biology and survival of patients fundamentally improved over the last years. Potential therapeutic approaches are shown in Figure 1. Especially in patients with de novo Her2-positive metastatic breast cancer, complete and durable responses with prolonged survival are often seen. This fuels the discussion concerning whether those are patients who might be treated with the intent to cure. Due to the development of new targeted agents, we as clinical oncologists are also confronted with a more intensive management of potential side effects. But although there are far more treatment options nowadays, Her2 heterogeneity and mechanisms of resistance during the treatment remain challenges of the treatment.[1, 2]

Discussion

First-Line Treatment

Two decades ago, adding trastuzumab to chemotherapy improved progression-free survival (PFS) and overall survival (OS) [3]. Due to cardiac toxicity, the combination with anthracyclines has been avoided for years. Later, the anti-Her2 antibody pertuzumab was introduced and

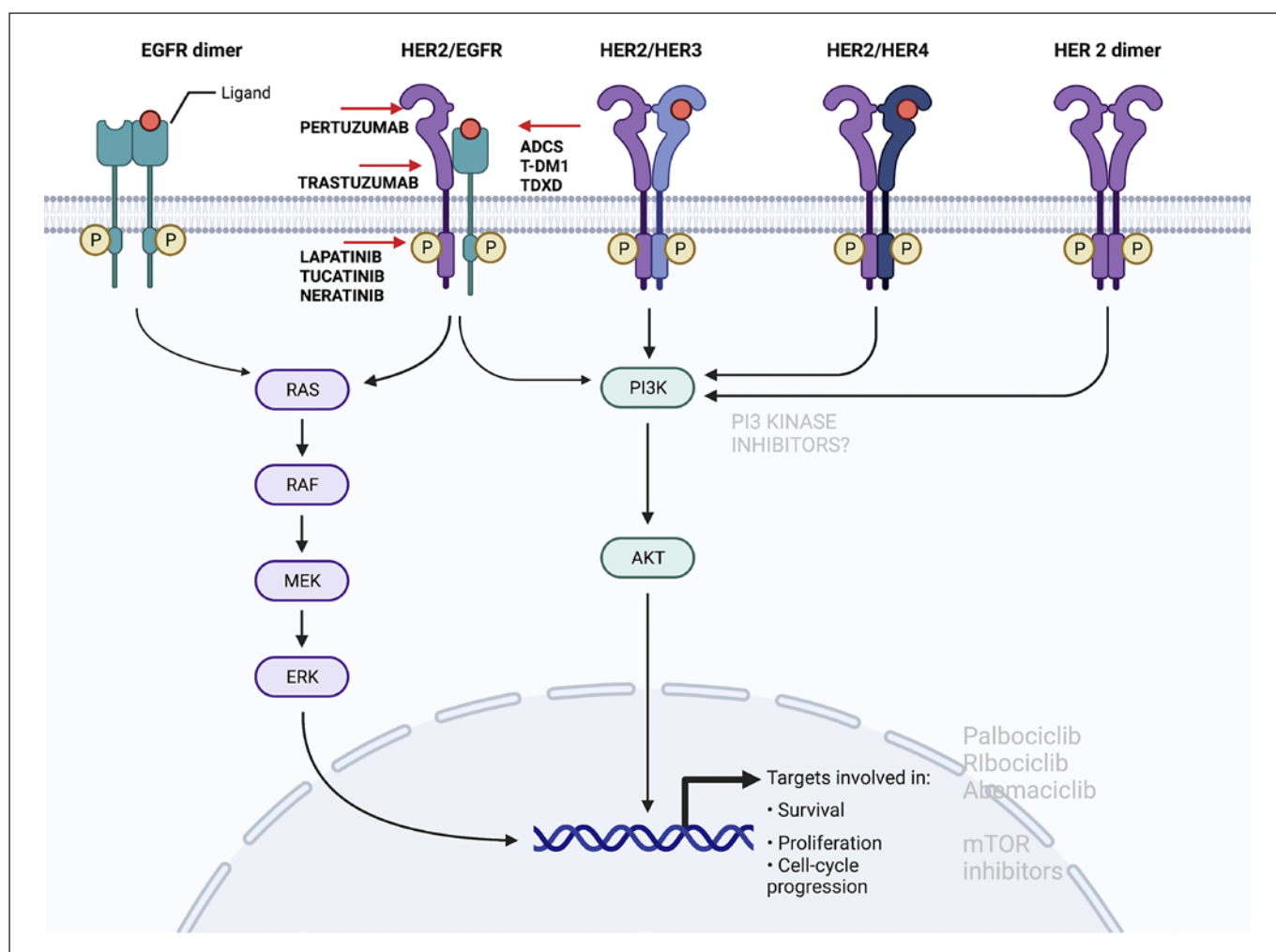


Fig. 1. Her signaling and Her2 targeting. Potential therapeutic approaches are antibodies (like pertuzumab and trastuzumab), antibody drug conjugates (T-DM1, T-DXd), TKIs (lapatinib, tucatinib, neratinib), and potential additional small molecules like CDK 4/6 inhibitors, mTOR inhibitors, or PI3 kinase inhibitors. The figure was created with BioRender.

investigated in the CLEOPATRA trial in combination with trastuzumab and docetaxel. Until now, this regimen is considered the gold standard in first-line treatment of Her2-positive metastatic breast cancer. Patients were randomized to receive either docetaxel/trastuzumab plus pertuzumab or placebo. Swain et al. published the end-of-study results in 2020 and reported, after a median follow-up of 99.9 months, a median OS of 57.1 months in the pertuzumab arm versus 40.8 months in the placebo group. The combination of metronomic oral cyclophosphamide plus trastuzumab and pertuzumab was investigated in older and frail patients. At a median follow-up of 20.7 months, the median PFS was 5.6 months under dual Her2 blockade versus 12.7 months under added oral chemotherapy [4, 5]. Based on the results of the VELVET study, a combination of trastuzumab, pertuzumab, and vinorelbine represents an alternative option for patients who may not be eligible for taxane-based treatment [6].

Antibody-Drug Conjugates

An ADC normally consists of a monoclonal antibody that is linked to a cytotoxic drug. The aim is to deliver the payload directly to the target cancer cells. The development of ADCs is one of the most important progresses in the treatment of metastatic breast cancer in general and particularly in the treatment of Her2-positive breast cancer.

The first ADC was trastuzumab emtansine (T-DM1) which is linked via a non-cleavable linker to DM-1, a microtubule inhibitor [7]. The implementation of T-DM1 as second-line treatment in Her2-positive metastatic breast cancer was a result of the phase III trial EMILIA. T-DM1 versus capecitabine plus lapatinib resulted in an improved PFS from 6.4 months to 9.6 months and an increased OS from 25.1 months to 30.9 months, thereby providing a more favorable toxicity profile [7, 8]. In the phase III trial THERESA, T-DM1 was compared with a

treatment of physician's choice in patients who were pretreated with trastuzumab and lapatinib. Again, PFS and OS improved [9]. In a third study, the MARIANNE trial, patients received either taxane plus trastuzumab, T-DM1 plus pertuzumab, or T-DM1 plus placebo. Interestingly, there was no significant difference in PFS in the three arms [10].

The second ADC that is approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) is trastuzumab deruxtecan (T-DXd). Although both share trastuzumab as the antibody, there are substantial pharmaceutical differences between these two drugs. Compared to T-DM1, it is characterized by a higher drug-to-antibody ratio and a cleavable linker. The payload is a topoisomerase I inhibitor which is membrane permeable. By crossing the cellular membrane, it is capable of killing surrounding cells regardless of their Her2-expression – this effect is called the bystander effect [11, 12]. First data of the phase I trial showed promising results in heavily pretreated patients with Her2-positive metastatic breast cancer but also in patients with Her2 score 1+ and 2+ without Her2 amplification. The objective response rate (ORR) in 111 patients was 59.5% with a median duration of response of 20.7 months. The most common toxicity was of hematological origin. However, 2 patients died due to interstitial lung disease (ILD) [13]. DESTINY-Breast01 was a phase 2 trial investigating T-DXd in a patient population ($n = 184$) that received a median of 6 previous lines including T-DM1. After a median follow-up of 11.1 months, an ORR of 60.9% and an overall disease control rate of 97.3% were achieved. Again, the incidence of ILD was not very low at 13.6% [14]. DESTINY-Breast03 was the next logical step: a head-to-head comparison of the two ADCs. Altogether, 524 patients were randomized to receive either T-DXd or T-DM1. The median PFS was not reached in the T-DXd arm and 6.8 months in the T-DM1 arm. At 12 months, 75.8% of the patients under T-DXd and 34.1% under T-DM1 were alive without disease progression with an impressive HR of 0.28. ILD or pneumonitis was diagnosed in 10.5% in the T-DXd arm with no incidence of grade 4 or 5. These outstanding results once again changed the treatment landscape of Her2-positive metastatic breast cancer. DESTINY-Breast03 led to FDA approval for T-DXd as second-line treatment after receiving an anti-Her2-based regimen in metastatic setting or in the adjuvant or neoadjuvant setting and a rapid disease progression during therapy or within 6 months afterward [15].

Tyrosine Kinase Inhibitors

TKIs inhibit cellular growth by binding to the cytoplasmic catalytic kinase domain of the Her family. Lapatinib, tucatinib, and neratinib are approved for the treat-

ment of Her2-positive metastatic breast cancer and differ in HER protein specificity, reversibility of binding, and molecular weight. Lapatinib binds reversibly to epidermal growth factor receptor type I (EGFR1), Her2, and Her4. It was the first approved TKI in this setting and the second Her2-targeted agent after trastuzumab [16]. In combination with capecitabine, the PFS was improved from 4.3 to 6.2 months versus capecitabine alone (HR 0.55). The numerical benefit in OS from 64.7 to 75.0 weeks was not statistically significant. Another phase 3 trial investigated lapatinib mono versus lapatinib plus trastuzumab after progression on trastuzumab. The median PFS in the combination arm was prolonged from 8.1 to 11.1 weeks (HR 0.74), the OS from 9.5 months to 14 months (HR 0.74). The most common adverse events (AEs) under lapatinib were diarrhea, nausea, and rash [17]. An improvement in PFS was also seen in combination with the aromatase inhibitor (AI) letrozole versus letrozole alone [18]. Neratinib, an irreversible pan-HER TKI targeting EGFR, Her2, and Her4, was firstly approved as monotherapy for extended adjuvant treatment of early Her2-positive breast cancer after completion of trastuzumab-based therapy [19]. In the metastatic setting, the combination of neratinib and capecitabine was compared with lapatinib and capecitabine in a phase 3 trial. The mean PFS at 24 months was 6.6 months for lapatinib and 8.8 months for neratinib, and the OS was similar with 22.2 months versus 24.0 months after a median follow-up of 29.9 months. The most common AE for neratinib plus capecitabine was diarrhea (all grades 83%, grade 3–4 24%) [20]. Based on these data, the FDA has granted approval for the metastatic setting. The newest and probably most promising TKI is tucatinib which is highly selective for Her2 with only minimal inhibition of EGFR. Despite its favorable toxicity profile, its advantage is that it crosses the blood-brain barrier. The phase II HER2CLIMB trial investigated tucatinib or placebo combined with trastuzumab and capecitabine in patients who received trastuzumab, pertuzumab, and T-DM1. Notably, this is the first larger trial that enrolled patients with active or treated brain metastases (BMs). The median PFS was prolonged by adding tucatinib from 5.6 to 7.8 months (HR 0.54). In the overall population of 612 patients, the median OS in the tucatinib arm was 21.9 months and 17.4 months in the placebo arm (HR 0.66). The ORR was higher under tucatinib (40.6%) than under placebo (22.8%). The HER2CLIMB regimen is now one of the preferred third-line treatments in metastatic Her2-positive breast cancer [2].

Brain Metastases

Between 30% and 55% of these patients develop BMs during their course of disease [21, 22]. Therefore, the presence of active or stable BM has also been incorpo-

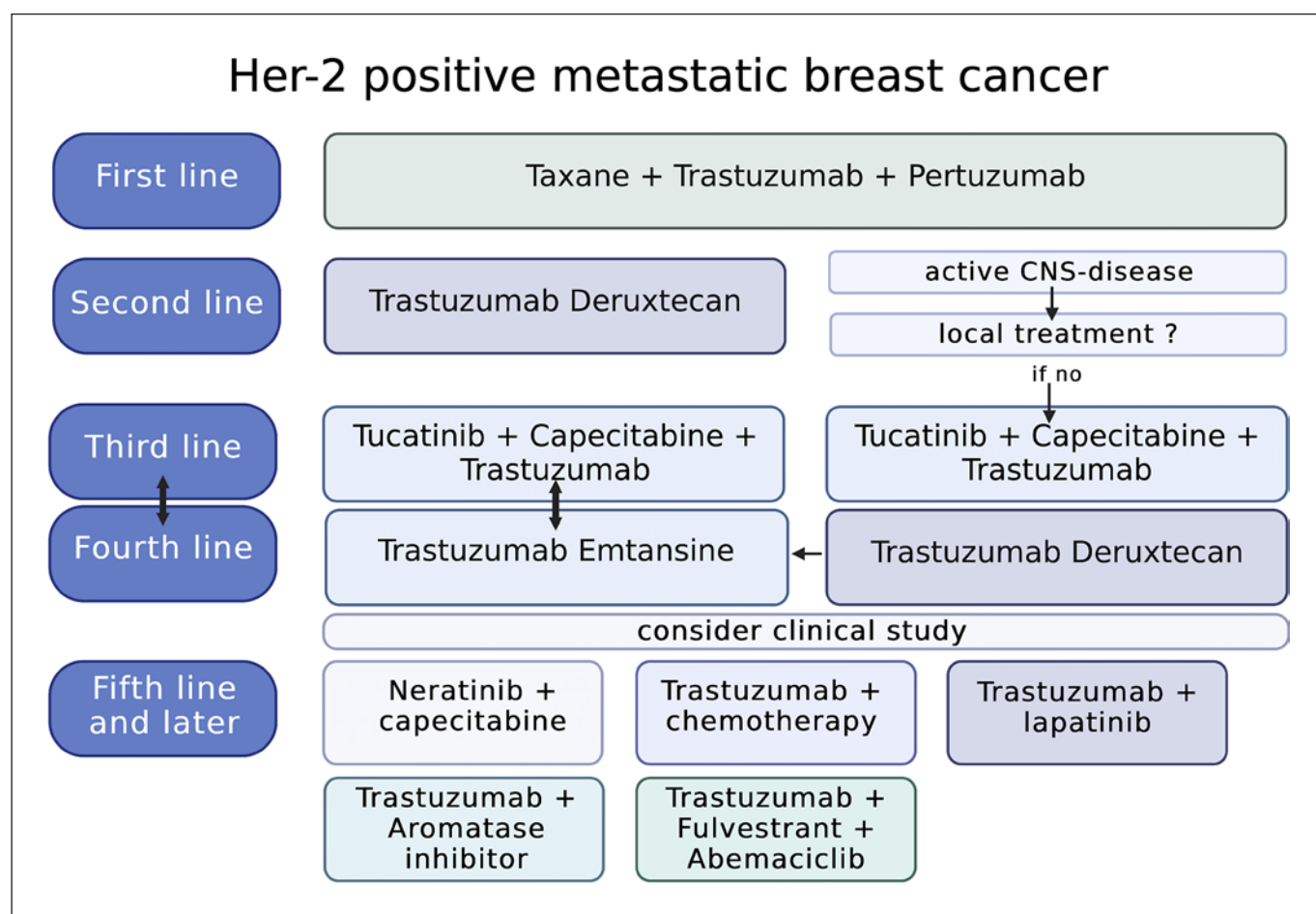


Fig. 2. Current treatment approaches for Her2-positive metastatic breast cancer (2022).

rated into international guidelines [23]. HER2CLIMB enrolled 291 patients with BM and differed between treated and stable, treated and progressing, and untreated. The OS was prolonged from 12 months to 18.1 months by adding tucatinib, and the intracranial ORR was 47.3% in the tucatinib arm versus 20% in the placebo arm [2]. The phase 2 trial TUXEDO-1 investigated the efficacy and safety of T-DXd in Her2-positive breast cancer patients with active BM. Of the 15 enrolled patients, 60% were progressing after previous local therapy and 60% were pretreated with T-DM1. Within the ITT population, an intracranial response rate of 73.3% was demonstrated. The median PFS was 14 months, and the OS was not reached [24]. These novel effective systemic treatment options for BMs strongly imply the need for early interdisciplinary interaction with neurosurgeons and radiologists, and only patients with intermediate need for local control due to symptoms should be treated locally first. Whole-brain irradiation seems to be reserved for later stages of disease.

Triple-Positive

About half of all patients with Her2-positive metastatic breast cancer are also hormone receptor positive. Two phase 3 trials showed no benefit of trastuzumab plus AIs in terms of OS [25, 26]. In the PERTAIN trial, patients received either trastuzumab plus pertuzumab plus an AI or trastuzumab plus AI after an optional induction chemotherapy. The PFS with the dual Her2 blockade was better compared to trastuzumab alone (18.9 vs. 15.8 months) [27]. In another trial, lapatinib/trastuzumab plus an AI achieved a longer PFS with 11 months versus 5.6 months with an AI plus either trastuzumab or lapatinib [28]. The MonarchHER study showed efficacy of the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor abemaciclib plus fulvestrant and trastuzumab. The control arm was either abemaciclib plus trastuzumab or standard chemotherapy plus trastuzumab. The triple combination demonstrated a significant benefit in PFS with 8.3 months versus 5.7 months in the chemotherapy arm with a tolerable safety profile [29]. An update of the numerical OS benefit was presented recently at the annual ESMO meeting 2022 [30].

Immune Checkpoint Inhibitors

Preclinical studies showed that Her2-positive breast cancer is immunogenic and trastuzumab has an immune-based mechanism of action [31]. Although there might be a high number of tumor-infiltrating lymphocytes as well as high levels of programmed death ligand 1 (PD-L1) in these tumors, data on the combination of Her2 blockade and PD-L1 inhibitors are not groundbreaking. The PAN-ACEA trial evaluated the combination of pembrolizumab and trastuzumab/pertuzumab. The ORR was 15%, and the disease control rate was 24% in PD-L1-positive Her2-positive breast tumors [32]. KATE2 investigated the addition of atezolizumab to T-DM1 versus T-DM1 alone. An exploratory analysis showed an improvement in PFS in terms of PD-L1 positivity [33]. There are several ongoing clinical trials on this topic.

Beyond Third Line

There are several treatment options beyond the third line including lapatinib (preferably in combination with capecitabine or trastuzumab), T-DM1, or neratinib. Continued anti-Her2-based therapy is the clinical standard for these patients, and trastuzumab (preferably in combination with different chemotherapies) beyond progression should be considered.

We are currently initiating the clinical trial NERHER (EudraCT number 2022-002582-15), aiming at evaluation of trastuzumab and neratinib with or without oral vinorelbine. The aim of the trial is to evaluate the efficacy of this combination in a later line setting in patients previously treated with tucatinib according to HER2CLIMB and/or T-DXd. If the trial achieves the primary endpoint and outperforms the historical 33% proportion of patients not progressing after 6 months of treatment with acceptable side effects and quality of life, this combination may consequentially become another treatment option. The current treatment approaches for metastatic Her2-positive breast cancer are shown in Figure 2.

What About a Cure?

Real-world data from France showed that the median OS from patients with Her2-positive metastatic breast cancer has dramatically improved from 39.1 months in 2008 to 58 months in 2013 [34]. Due to the development of new drugs and improvement of long-term outcomes, it is increasingly probable to treat these patients with curative intent or at least to achieve long-term control. Between 5% and 50% of our patients achieve complete remission when undergoing Her2-targeted treatment, which is correlated with an improved OS [35, 36]. Several factors such as de novo stage IV disease, younger age, good performance status, positive response to trastuzumab treatment, hormone receptor co-expression, and non-visceral metastasis were associated with a better long-

term outcome in different trials [37, 38]. One more question regarding the treatment of these patients with a long-time outcome relates to the optimal duration of Her2-targeted therapy. Studies investigating the discontinuation of treatment are ongoing. The further improvement of treatment strategies, long-term follow-up of ongoing prospective trials, and the search for predictive factors of a good outcome will contribute to a better understanding of metastatic Her2-positive disease and answering the question of whether a cure will be possible one day.

Future Outlooks

The introduction of Her2-targeted agents has revolutionized the outcomes for our patients with Her2-positive metastatic breast cancer. One newcomer is margetuximab, an anti-Her2 antibody with a modified Fc domain, that has a stronger binding affinity to the activating CD16A receptors on immune cells compared to trastuzumab. It has a lower binding affinity to the inhibitory Fc receptors of the antigen-presenting cells which may lead to a better immune response. Its efficacy was investigated in the SOPHIA trial, where trastuzumab plus chemotherapy was compared to margetuximab plus chemotherapy in patients who had received 2 or more prior lines with anti-Her2 therapies. The median PFS under margetuximab was 5.8 months versus 4.9 months under trastuzumab. This marginal gain in PFS did not translate in a significantly better OS. Margetuximab seems to have potential for later line Her2-positive breast cancers with resistance to trastuzumab and special genotypes [39]. Trastuzumab duocarmazine is a novel ADC investigated in the phase 3 TULIP trial compared to a treatment of physician's choice in patients with Her2-positive metastatic breast cancer who were pretreated with 2 or more lines or with T-DM1. The median PFS with trastuzumab duocarmazine was 7.0 months versus 4.9 months in the control arm (HR 0.64). The median OS was 20.4 months with trastuzumab duocarmazine and 16.3 months with treatment of physician's choice (HR 0.83). The most common grade 3 or higher AEs were keratitis, conjunctivitis, and neutropenia [40]. Another newcomer is pyrotinib, an irreversible pan-Her TKI available in China. In a phase 2 trial, pyrotinib plus capecitabine was tested against lapatinib plus capecitabine. The median PFS was prolonged from 7.0 months under lapatinib to 18.1 months under pyrotinib. About one-half of the patients were trastuzumab-pretreated, and none of them received pertuzumab or T-DM1 prior to enrolling in the study [41]. Studies investigating novel anti-Her2 antibodies, new ADCs as well as promising combination strategies (PI3K inhibitors, CDK4/6 inhibitors) are on the horizon and will hopefully contribute to further improvement of outcomes.

Conclusion

The natural history of Her2-positive metastatic breast cancer is being changed due to development of new targeted agents. The implementation of ADCs and achievements in the treatment of BMs have been milestones in recent years. We are on the right way to eradicate cancer cells in order to lead a long and normal life with this disease.

Conflict of Interest Statement

C.S. received honoraria for consulting or advisory role and travel/accommodations from Roche, Novartis, Pfizer, Lilly, AstraZeneca, Daiichi Sanky, and Astellas. M.B. reports personal fees/travel

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Author Contributions

C.S. and M.B. wrote the review article.

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