Update Breast Cancer 2022 Part 2 – Advanced Stage Breast Cancer

Update Mammakarzinom 2022 Teil 2 – Brustkrebs in fortgeschrittenen Krankheitsstadien

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**ABSTRACT**

For patients with advanced breast cancer, several novel therapies have emerged in recent years, including CDK4/6 inhibitors, immune checkpoint inhibitors, PARP inhibitors, alpelisib, tucatinib and trastuzumab-dur dxtecan, and sacituzumab-govitecan, which have transformed and expanded the therapeutic landscape for patients with advanced breast cancer. Some of these substances have now been approved for use in the early stages of the disease, or are expected to be approved in the near future, so the therapeutic landscape will change once again. Therefore, current scientific efforts are focused on the introduction of new substances and understanding their mechanisms of progression and efficacy. This review summarizes recent developments with reference to recent publications and conferences. Findings on the treatment of patients with HER2-positive breast cancer and brain metastases are presented, as are a number of studies looking at biomarkers in patients with HER2-negative, hormone receptor-positive breast cancer. In particular, the introduction of oral selective estrogen receptor degraders provides new opportunities to establish biomarker-based therapy. Molecular diagnostics is establishing itself as a diagnostic marker and parameter of progression.

**ZUSAMMENFASSUNG**


**Introduction**

With increasing knowledge of resistance mechanisms of established treatments such as CDK4/6 inhibitors and the introduction of new substances such as oral SERDs, the question of how biomarkers can be used to improve clinical practice or individualized treatment planning is of growing concern. The scientific community is also focused on understanding which HER2-positive patient groups will benefit most from the new treatments. Many of the new findings are linked to biomarkers, which are presented below.

**HR+ HER2−: The First SERD in a Phase III Trial and Biomarker in CDK4/6 Inhibitors**

**ESR1 mutations for selection of endocrine counterpart for treatment with SERDs**

With mounting evidence that an ESR1 mutation may be a resistance marker for aromatase inhibitor therapy [1], it is essential to understand whether this biomarker can be of clinical relevance. A mutation in ESR1 leads to the estrogen receptor being constitutively switched on, regardless of whether the receptor complex is activated by estrogen [1]. In this situation, treatment with aromatase inhibitors or a selective estrogen receptor modulator (SERM) cannot downregulate the activity of the estrogen receptor. However, SERDs are thought to be able to downregulate both the wild-type and mutant forms of the estrogen receptor (Fig. 1). ESR1 mutations are known to occur in only about 5% of cases in patients without prior treatment, whereas they are detected in up to 30–40% of cases in patients whose disease had progressed to or have relapsed on an aromatase inhibitor [2, 3]. It must therefore be assumed that ESR1 mutations accumulate during treatment with aromatase inhibitors and that this is one of the resistance mechanisms that reduces the effectiveness of aromatase inhibitors.

One of the trials investigating the clinical utility of this approach is the PADA-1 trial [4]. The PADA-1 trial included patients treated with palbociclib and an aromatase inhibitor as first-line therapy without evidence of endocrine resistance. During treatment, circulating tumor DNA in blood (ctDNA) was tested for evidence of an ESR1 mutation before treatment, 1 month after the start of treatment and every 2 months thereafter. Only a few relevant mutations have been described for the ESR1 gene, so geno-
typing can be restricted to a few genomic loci. In the case of the PADA-1 trial, mutations were determined at the following locations: E380, P535, L536, Y537, D538 [4].

If ESR1 mutations were found and there was no clinical evidence of progression, patients were randomized to one of two treatment arms. In one arm, the previous treatment was continued, while in the experimental arm, endocrine treatment was substituted for the SERD fulvestrant while continuing palbociclib.

The analysis of progression-free survival showed that patients who switched to fulvestrant had a median PFS of 11.9 months (95% CI: 9.1–13.6), which was significantly longer than patients who continued treatment with an aromatase inhibitor. In this group, the median PFS was 5.7 months (95% CI: 3.9–7.5). The hazard ratio was 0.61 (95% CI: 0.43–0.86) [4]. Overall survival data have not yet been presented [4]. Patients who were not switched at the time of “molecular progression” went on to receive fulvestrant and palbociclib once progression was detectable on imaging; PFS in this group was 3.5 months (95% CI: 2.7–5.1), so the actual gain in PFS in the intervention arm was only 2.7 months. The question therefore arises as to whether the patients in the intervention arm actually benefited or whether they were simply switched over earlier. The concept of “molecular progression” has been clinically validated for the first time in PADA-1 and proof-of-concept has been obtained. However, it is too early for clinical application, and it remains to be seen whether ongoing trials with more effective interventions will provide a clearer picture.

Currently, several trial programs are pursuing a similar strategy with oral SERDs. For example, one such ongoing trial is SERENA-6 [5].

**EMERALD trial published**

With a large number of SERDs currently in clinical development [6, 7], the first phase III trial, the EMERALD trial, has now been published [8]. This study is of particular interest not only in terms of whether SERD treatment can overcome endocrine resistance based on an ESR1 mutation, but also in terms of a comparison between the oral SERD elacestrant and fulvestrant. The EMERALD trial included patients with advanced breast cancer who had previously been treated with at least one CDK4/6 inhibitor plus endocrine treatment. However, patients who had received additional endocrine treatment or prior chemotherapy were also eligible. After randomization, patients were treated with either the SERD elacestrant or standard treatment (fulvestrant, exemestane, letrozole, or anastrozole) [8]. Of particular interest are the stratification factors of the ESR1 mutation in circulating ctDNA and prior treatment with fulvestrant.

In the overall analysis, elacestrant was shown to improve progression-free survival compared with standard treatment, with a hazard ratio of 0.697 (95% CI: 0.552–0.880). However, median PFS only improved from 1.9 months to 2.8 months in this heavily pre-exposed population. Also, more than 40% of the patients treated with elacestrant had primary progression. In the group of patients with an ESR1 mutation in ctDNA, median PFS improved from 1.9 months to 3.8 months (HR = 0.546; 95% CI: 0.387–0.768). Comparing patients treated with elacestrant to patients on fulvestrant therapy, the HR was 0.684 (95% CI: 0.521–0.897) in the overall group and 0.504 (95% CI: 0.341–0.741) in the group with ESR1 mutation [8].

It was therefore shown that in this heavily pre-exposed population, the oral SERD elacestrant was more effective than fulvestrant or treatment with aromatase inhibitors. However, in a population
like this, primary progression rates are very high and median progression-free times are very short, so it is not possible to make a robust assessment of whether endocrine resistance can be overcome with this treatment. However, the results are certainly promising, especially for future combination therapies, for which elacestrant may be a better candidate than intramuscular fulvestrant. Studies carried out under previous treatment regimens will show whether oral SERDs such as elacestrant bring substantial further benefit to the treatment of patients with HR+, HER2− breast cancer.

Interim analyses in the MONARCH-3 trial

The Summary of Product Characteristics, published in January 2022, includes a new interim analysis of the MONARCH-3 trial [9], which compared abemaciclib plus an aromatase inhibitor and aromatase inhibitor alone as first-line therapy. The most recent interim analysis of 255 deaths showed a median OS of 54.5 months with an aromatase inhibitor alone, and 67.1 months with combination therapy (Fig. 2). This corresponded to a hazard ratio of 0.754 (95% CI: 0.584–0.974; p = 0.0301). The p-value did not achieve the threshold for significance [9] required for the interim analysis, so the next analysis is awaited.

CDK4/6 inhibitor therapy and BRCA mutations

Based on retrospective analyses, it has been suggested that a germline mutation in BRCA1/2 (gBRCA1/2) may reduce the effectiveness of CDK4/6 inhibitors. When comparing gBRCA1/2 mutation carriers and patients without mutations, these retrospective analyses showed a hazard ratio of 1.50 (95% CI 1.06–2.14) [10]. The same question was now studied in a high-quality cohort of patients with advanced breast cancer using retrospective-prospective data. A total of 223 gBRCA1/2 mutations were detected in 4460 patients (101 in BRCA1 and 122 in BRCA2). This resulted in a mutation rate of 4.8%, which is similar to the figures from a large real-world analysis of gBRCA1/2 mutation rates [11].

The aforementioned cohort included a total of 1005 patients who had been treated with a CDK4/6 inhibitor. 45 patients with a gBRCA2 mutation had worse PFS with a hazard ratio of 2.12 (95% CI: 1.48–3.03). When restricted to patients treated as part of first-line therapy (n = 439), patients with a gBRCA2 mutation (n = 24) also had worse PFS (HR = 2.32; 95% CI: 1.38–3.91).

Overall, however, the patients treated in this cohort appeared to have a worse prognosis. The median PFS for first-line therapy in wild-type patients was 14.7 months. Although this analysis provides good evidence that a gBRCA1/2 mutation is associated with somewhat poorer efficacy with a CDK4/6 inhibitor, the results should be confirmed before they are applied more broadly. However, in the presence of a gBRCA1/2 mutation, this study provides good arguments for case-by-case decision-making for possibly starting first-line therapy with PARP inhibitors.

Mutation analysis of ctDNA and the efficacy of ribociclib therapy

The excellent outcomes seen with CDK4/6 inhibitors in treating metastatic disease [12–27] highlight the importance of this treatment for patients with advanced HER2−/HR+ breast cancer. It has become the gold standard in first-line therapy [28] and has largely replaced endocrine monotherapy and chemotherapy as
first-line therapy [29]. It is likely that drug development will continue to be guided by this standard for many years to come. This makes it all the more important to increase our understanding of resistance mechanisms and molecular patterns of efficacy. This will help identify new drug targets and establish surveillance mechanisms. One trial with these objectives is BioItaLEE, the preliminary results of which have been published [30].

The BioItaLEE trial included patients treated with ribociclib and letrozole in an endocrine-sensitive setting during first-line therapy. Extensive biomarker sampling was performed before treatment, after 15 days, and on the first day of the second cycle. Using the blood samples, exons from a total of 39 breast cancer-related genes were sequenced. A total of 263 patients were included in the trial. In one of the genes analyzed, mutations were found in 113 patients. Patients without a genetic mutation had a significantly better prognosis, with a hazard ratio of 0.41 (95% CI: 0.27–0.61) [30]. In 49 of the patients who had a mutation prior to starting treatment, the treatment was able to eliminate the ctDNA carrying the mutation in the blood. By grouping the patients according to their mutation status before treatment and after 15 days, it was possible to identify different prognostic groups:

- no mutation before treatment → no mutation after 15 days (n = 115)
- no mutation before treatment → mutations after 15 days (n = 19)
- mutations before treatment → no mutation after 15 days (n = 44)
- mutations before treatment → mutations after 15 days (n = 60)

Patients with persistent mutations had the worst prognosis with a median PFS of 12.3 months. Patients with no mutations at either point in time had the best prognosis, with a median follow-up of 26.9 months and a median PFS in the overall population of 23.4 months in the group that had not yet attained median PFS. Median progression-free survival is shown in Fig. 3 [30].

Future studies are needed to determine whether other treatments may be a better option for patients with a poor prognosis. It must be kept in mind that CDK4/6 inhibitors are a very effective treatment with an acceptable side effect profile and that a worse prognosis based on biomarkers does not automatically imply that a better outcome can be achieved with an alternative treatment.

![Kaplan-Meier curve of PFS (months) by status at BL and D15](image-url)
Choosing Treatment After Biomarker Testing

The use of biomarkers to choose a targeted treatment instead of chemotherapy

As our knowledge of biomarkers increases and potential treatments emerge based on them, the question arises as to whether the available treatments and knowledge of so-called “actionable genetic variants” (mutations/amplifications/translocations that indicate the efficacy of a targeted treatment) are sufficient to decide which patients need chemotherapy and which patients would be better served by a targeted treatment.

One trial that investigated this is SAFIR02 [31]. Patients with advanced HER2-negative breast cancer who were stable and without progression after 6–8 cycles of chemotherapy were enrolled in this trial. These patients were tested for the following so-called “actionable genetic alterations” for the following treatments: alpelisib, olaparib, capivasertib, vistusertib, AZD8931, vandetanib, bicalutamide, AZD4547 and selumetinib. However, it must be kept in mind that there is a probable ESCAT category I or II association for only a proportion of these drugs [32]. According to these ESCAT I and II categories, the following targeted treatments were administered in the presence of the corresponding mutations (number of patients treated in parentheses): Olaparib for a gBRCA1/2 mutation (n = 60), alpelisib for a PIK3CA mutation (n = 31), capivasertib for an AKT1 mutation (n = 21), and sapitinib for an EGR mutation (n = 3). In this group, patients treated with targeted treatment had a longer median PFS of 9.1 months (95% CI: 7.1–9.8) compared with the group in which chemotherapy was continued (median PFS: 2.8 months; 95% CI: 2.1–4.8). It should be noted, however, that the patients who accounted for a large proportion of the overall effect were those treated with olaparib (HR = 0.29; 95% CI: 0.17–0.49) [31].

In the group of patients treated with targeted therapy based on proven mutations that did not fall into ESCAT categories I or II, no improvement in PFS was observed compared with continuing chemotherapy (HR = 1.15; 95% CI: 0.76–1.75). In this respect, SAFIR02 represents an important proof-of-concept for molecular tumor boards, but also further clarifies that this is limited exclusively to ESCAT tier I or II alterations.

In principle, the SAFIR02 trial confirms the results of the OLYMpiAD trial, in which patients treated with olaparib monotherapy had better PFS than patients treated with chemotherapy [33]. However, the SAFIR02 trial shows that it may also be appropriate to switch from chemotherapy to which patients had responded or even stable disease to treatment with olaparib in the case of a gBRCA1/2 mutation.

Role of PD-L1 expression on progression-free survival and overall survival in the KEYNOTE-355 trial

The KEYNOTE-355 trial evaluated the addition of pembrolizumab to standard chemotherapies in the first advanced line of therapy in patients with metastatic triple-negative breast cancer (TNBC) [34]. Due to the study design, the primary analysis focused on patients with a PD-L1 expression of ≥ 10 as determined by the Combined Positive Score (CPS). However, patients with lower PD-L1 expression were also included. In this context, the question is whether patients with lower levels of PD-L1 expression might also benefit from treatment with pembrolizumab, taking account of its side effects. In this context, extensive analyses of KEYNOTE-355 have now been published [35].

In the overall population of KEYNOTE-355 patients regardless of PD-L1 expression, median progression-free survival improved from 5.6 months to 7.5 months (HR = 0.82; 95% CI: 0.70–0.98), while overall survival improved from 15.5 months to 27.2 months (HR = 0.89; 95% CI: 0.76–1.05) [34]. In the pre-specified population of patients with a CPS of ≥ 10, analyses showed statistically significant superiority of pembrolizumab combination therapy with respect to both outcome parameters [34].

A Fig. 4 shows the hazard ratios for PFS and OS as a function of PD-L1 expression (CPS < 1; CPS 1–9; CPS 10–19; and CPS ≥ 20). There is evidently a consistent improvement in the hazard ratio in favor of pembrolizumab therapy in progression-free survival from 1.09 at a CPS of 0 to a HR of 0.62 at a CPS of ≥ 20 [34]. These significant effects could not be shown with respect to overall survival. This showed hazard ratios of approximately 1 in patients up
to a CPS of 0–9 and an HR of approximately 0.7 in both groups with a CPS ≥10 [34]. Thus, the established CPS cut-off of 10, at which it can be assumed that a benefit in terms of overall survival and progression-free survival has been achieved, therefore seems to be appropriate.

Triple-negative Patients – Further Development of Antibody-Drug Conjugate

A new ADC with Trop2 as the target structure

The impressive results of therapy with the anti-Trop2 antibody-drug conjugate (ADC) sacituzumab govitcan in patients with heavily pretreated advanced TNBC in the ASCENT trial have focused attention on this target. In the ASCENT trial, in patients with advanced triple-negative breast cancer, median progression-free survival was significantly improved with sacituzumab govitcan compared with chemotherapy of the physician’s choice (capecitabine or eribulin or vinorelbine or gemcitabine) (HR = 0.41; 95% CI: 0.32–0.52) and median overall survival approximately doubled from 6.7 months to 12.1 months (HR = 0.48; 95% CI: 0.38–0.59) [36].

Trop2 is an antigen that is overexpressed in some cancers such as breast cancer, some thyroid cancers, pancreatic cancer, colon cancer, urothelial cancer, and other tumors [37–39]. It is thought to be involved in various signal transduction pathways (Fig. 5).

Some ADCs are currently in clinical development [40]. Data from a study investigating a different ADC, datopotamab deruxtecan, have now been published [41]. Similar to sacituzumab govitcan, the payload is a topoisomerase I inhibitor. In the TROPION-PanTumor01 trial, 44 patients with advanced triple-negative breast cancer were treated, among other cancer types, 30 (68%) of whom had undergone two or more prior treatments for advanced TNBC [41]. A response was seen in 15 patients (34%) and 17 had stable disease. Interestingly, 14 of 27 patients (52%) who had already been pretreated with another topoisomerase I inhibitor-based ADC also responded to datopotamab deruxtecan. Nausea/vomiting and stomatitis were the most common side effects, whereas hematological toxicity and diarrhea were uncommon, occurring in only 15–20% [41].

In the ASCENT trial of sacituzumab govitcan, the response rate was 31%, which is very similar to the response rate seen in the TROPION-PanTumor01 trial [36,41]. It is hoped that ADCs of this kind will be developed for earlier disease stages as soon as possible. Sacituzumab govitcan, for example, is already being...
Brain Metastases in Focus in Patients with HER2+ aBC

Brain metastases in the HER2CLIMB trial

Data from the HER2CLIMB trial, which investigated therapy with tucatinib, trastuzumab, and chemotherapy in the treatment setting after trastuzumab/pertuzumab and T-DM1, showed an improvement in PFS and OS compared with trastuzumab and chemotherapy even in the primary analysis. This study was interesting in that it also enrolled patients who had newly diagnosed or progressive ("active") cerebral metastasis without prior local treatment when it was not immediately necessary. The presence of brain metastases (yes vs. no) was also a preplanned stratification factor. In addition, patients with brain metastases at baseline were divided into those with active and stable brain metastases. All patients underwent MRI of the brain at baseline and were assigned to the following groups: [treated and stable], i.e. patients who had received prior local treatment and had not progressed at the time of enrollment; treatment may have been given during the screening period; and [treated and progressive], i.e. patients who had been treated for brain metastases in the past and had progressed at the time of enrollment. Patients who had not received local pretreatment were also included in this group. In addition, the inclusion and exclusion criteria listed in Table 1 were applied. A total of 117 patients with stable brain metastases and 174 patients with active brain metastases were enrolled in the HER2CLIMB trial.

Using this categorization, patients with active brain metastases treated with trastuzumab and chemotherapy had a median PFS of 4.1 months (95% CI: 2.9–5.6) and patients with stable brain metastases had a median PFS of 5.6 months (95% CI: 3.0–9.5). In

| Table 1 | Original texts for the inclusion and exclusion criteria related to brain metastases in the DESTINY-B03 and HER2CLIMB trials (according to [46] and [47]). |

<table>
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<th>Original text Inclusion criteria HER2CLIMB trial</th>
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<tr>
<td><strong>CNS Inclusion</strong> – Based on screening contrast brain magnetic resonance imaging (MRI), patients must have one of the following:</td>
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<tr>
<td>1. No evidence of brain metastases</td>
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<tr>
<td>2. Untreated brain metastases not needing immediate local therapy. For patients with untreated CNS lesions &gt; 2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrollment</td>
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<tr>
<td>3. Previously treated brain metastases</td>
</tr>
<tr>
<td>a. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy, provided that there is no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator</td>
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<tr>
<td>b. Patients treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if all of the following criteria are met:</td>
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<tr>
<td>i. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days</td>
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<td>ii. Other sites of disease assessable by RECIST 1.1 are present</td>
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<td>4. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions</td>
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<td><strong>CNS Exclusion</strong> – Based on screening brain MRI, patients must not have any of the following:</td>
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<tr>
<td>1. Any untreated brain lesions &gt; 2.0 cm in size, unless discussed with medical monitor and approval for enrollment is given</td>
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<tr>
<td>2. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of ≥ 2 mg of dexamethasone (or equivalent). However, patients on a chronic stable dose of ≤ 2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the medical monitor</td>
</tr>
<tr>
<td>3. Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to patient (e.g. brain stem lesions). Patients who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria 19b</td>
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<tr>
<td>4. Known or suspected leptomeningeal disease (LMD) as documented by the investigator</td>
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<td>5. Have poorly controlled (&gt; 1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy</td>
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<th>Original text Exclusion criteria DESTINY-B03 trial</th>
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<td>Spinal cord compression or clinically active central nervous system (CNS) metastases, defined as untreated or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.</td>
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<tr>
<td>• Subjects with clinically inactive brain metastases may be included in the study.</td>
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<tr>
<td>• Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 wk must have elapsed between the end of whole brain radiotherapy and study enrollment.</td>
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tested in the post-neoadjuvant setting in the SASCIA trial, which is currently recruiting patients [42].
both populations, PFS was improved by tucatinib with a hazard ratio of 0.36 (95% CI: 0.22–0.57) for patients with active brain metastases and a hazard ratio of 0.31 (95% CI: 0.14–0.67) for patients with stable brain metastases [43].

Detailed data have now been published for patients who had brain metastases at the start of treatment in the DESTINY-B03 trial (n = 82) [44]. The exclusion criteria relating to brain metastases are listed in ▶Table 1. Accordingly, patients with untreated or symptomatic brain metastases were not eligible for inclusion in the study. Nevertheless, patients in the comparator arm (T-DM1) with these criteria for brain metastases had a median PFS of only 3 months (95% CI: 2.8–5.8). The median PFS for patients with brain metastases was improved by T-DXd to 20.9 months (95% CI: 8.7–36.6) (HR = 0.25; 95% CI: 0.13–0.45) [44]. Of 82 patients with brain metastases, 72 had a target lesion in the brain, 36 in the T-DXd arm and 36 in the T-DM1 arm. In the T-DXd arm, 10 patients (27.8%) achieved complete remission compared with one patient (2.8%) in the T-DM1 arm [44].

Without comparing HER2CLIMB and DESTINY-B03 in terms of the efficacy of their investigational substances, patients treated with T-DM1 in the DESTINY-B03 trial do not appear to have been a more stable population in terms of progression than patients treated in the comparator arm of the HER2CLIMB trial. In quantitative terms, the median PFS in the DESTINY-B03 trial for this subgroup in the comparator arm was even shorter (3 months) than in the HER2CLIMB trial (4.1 months). It should be noted that the population of patients in the DESTINY-B03 trial was much smaller than in the HER2CLIMB trial, so the data on brain metastases will certainly require improvement. It is also unclear whether therapy with T-DM1 may be less effective than therapy with trastuzumab and chemotherapy. In the KAMILLA trial, patients with brain metastases predominantly after trastuzumab pretreatment had a response rate of 21.4% and a median PFS of 5.5 months (95% CI: 5.3–5.6 months) [45]. In the DESTINY-B03 trial, the response rate with T-DM1 was 33.4% and the median PFS was 3.0 months [44].

Future Perspectives
In the years to come, biomarker data on CDK4/6 inhibitors will increase significantly, as will information on oral SERDs. At present, it is unclear whether a mutation in ESR1 can be used in clinical settings to select patients who have resistance to aromatase inhibitors, and whether treatment with SERDs is more appropriate in these patients. The approval of the first CDK4/6 inhibitor in the adjuvant setting and the adoption of the new anti-HER2 drugs in the treatment of patients with early stage disease will result in changes in therapeutic settings in the years to come. The rapid pace at which new innovations are emerging is in itself remarkable.

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Conflict of Interest
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S. B. has no conflict of interest.
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