Update Breast Cancer 2022 Part 6 – Advanced-Stage Breast Cancer

Update Mammakarzinom 2022 Teil 6 – Brustkrebs in fortgeschrittenen Krankheitsstadien

OPEN ACCESS

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ABSTRACT

Large-scale study programs on CDK4/6 inhibitors, targeted therapies, and antibody–drug conjugates launched in recent years have yielded results from current studies which are now being published in journals and presented at international conferences. In this context, new results are available from the major CDK4/6 inhibitor studies. Also, an increasing amount of data is being published from large-scale genomic studies on efficacy and resistance mechanisms in patients treated with CDK4/6 inhibitors. These results now form the basis for further research plans to investigate combination therapies and treatment sequencing. Based on the latest published results, sacituzumab govitecan is now available as a second antibody–drug conjugate; this brings an advantage in terms of overall survival for patients with hormone receptor-positive (HRpos)/HER2-negative (HER2neg) breast cancer. In this review article, we summarize the latest developments and place them in context according to the current status of research.

ZUSAMMENFASSUNG

Die in den letzten Jahren begonnenen großen Studienprogramme zu den CDK4/6-Inhibitoren, den zielgerichteten Therapien und den Antikörper-Medikament-Konjugaten resultieren in Ergebnisse, die von aktuellen Studien auf internationalen Kongressen und Fachzeitschriften veröffentlicht werden. In diesem Zusammenhang sind neue Ergebnisse der großen CDK4/6-Inhibitor-Studien verfügbar. Auch werden zunehmend Daten von großen genomischen Studien zu Effektivitäts- und Resistenzmechanismen für Patientinnen, die mit CDK4/6-Inhibitoren behandelt worden sind, veröffentlicht. Basierend auf diesen Ergebnissen sollten nicht zuletzt Studien in Bezug auf Kombinationspartner und Therapiesequenzen geplant werden. Mit Sacituzumab Govitecan ist aufgrund neuester Veröffentlichungen nun ein zweites Antikörper-Medikament-Konjugat vorhanden, das bei hormonrezeptorpositiven (HRpos)/HER2-negativen (HER2neg) Patientinnen einen Gesamtüberlebensvorteil mit sich bringt. Diese Übersichtsarbeit fasst die neuesten Entwicklungen zusammen und ordnet sie in den aktuellen Forschungsstand ein.

Introduction

CDK4/6 inhibitors have become established as the new standard in first-line treatment for advanced or metastatic disease in patients with HRpos tumors. Data are being successively accumulated which help us to better understand the mechanisms of resistance and efficacy. Extensive genomic analysis gives new insights into the heterogeneity of the disease course in patients treated with CDK4/6 inhibitors. It is precisely these insights which may, in the coming years, determine the treatment sequences for patients with advanced-stage breast carcinoma. Moreover, the new antibody–drug conjugates represent the most cutting-edge innovations for patients with advanced-stage breast cancer. A whole series of new results have been published for both trastuzumab deruxtecan (T-DXd) and for sacituzumab govitecan.

Hormone Receptor-Positive Disease and CDK4/6 Inhibitors

Monarch 3

Among the large-scale, randomized phase III studies on palbociclib, ribociclib, and abemaciclib in patients with metastatic disease [1–16], the Monarch 3 study on first-line therapy with abemaciclib is the only one for which a final analysis of overall survival is not yet available. This situation did not change at this year's ESMO 2022 Congress; however, an extensive, planned interim analysis of the Monarch 3 study was presented at this conference [17], after parts of the data had already been published in the technical information for this product at the start of 2022 [18]. The interim analysis presented in this context related to overall survival; the database used was closed in July 2021, and the median observation period was 5.8 years. With a p-value of 0.0301, the results are not yet statistically significant. Median overall survival was improved numerically, from 54.5 to 67.1 months. This corresponded to a hazard ratio (HR) of 0.754 (95% CI: 0.584–0.974) [17]. In the subgroup analysis, there was only one subgroup in which no consistent effect could be seen. The effect was most pronounced in the group of patients with negative progesterone receptor status (HR = 0.425; 95% CI: 0.368–0.702), while in the group with progesterone receptor-positive tumors, the effect achieved a hazard ratio of only 0.919 (95% CI: 0.682–1.238). These differences give rise to a number of hypotheses which may be investigated further in future studies. It remains to note that there is currently a discussion around the value of progesterone receptor determination, with some arguing that it should instead be used as a prognosis factor for patients with positive estrogen receptor status [19]. An update on progression-free survival, with the same database closure date, was also presented. In this case, the HR was 0.518 (95% CI: 0.415–0.648), which corresponds to an extension of the median progression-free survival (PFS) time from 14.8 months to 29.0 months. Furthermore, 26.7% of patients treated with abemaciclib were still progression-free after five years, while for patients receiving monotherapy with aromatase inhibitors, this figure was only 9.6% [17]. An-

other piece of clinically relevant information from this analysis of long-term follow-up data is that no additional safety signals could be seen, even with long-term exposure. The final analysis is expected to appear in 2023.

DAWNA-2

Compared to other CDK4/6 inhibitors, dalpiciclib, a CDK4/6 inhibitor which has not been approved for the European market, shows an inhibitory effect similarly strong to that of palbociclib, with a CDK4 : CDK6 IC50 ratio of 0.8. In preclinical trials, it showed potent inhibition of cell growth [20, 21]. In previously published data from the DAWNA-1 study, patients showing a certain degree of endocrine resistance were treated with fulvestrant or fulvestrant + dalpiciclib [22]. The DAWNA-1 study was able to show an improvement in PFS. Now the results from the DAWNA-2 study have been presented; similar to the Monaleesa-2, Paloma-2 and Monarch 3 studies, this study focused on patients receiving first-line therapy for advanced stage disease [23]. The patients were randomized at a ratio of 1 : 2 to receive either letrozole or anastrozole, or therapy with an aromatase inhibitor plus dalpiciclib. The primary study goal was progression-free survival.

In this study, the median progression-free survival under endocrine monotherapy was increased from 18.2 months to 30.6 months. This corresponded to a hazard ratio of 0.51 (95 % CI: 0.38–0.69) [23]. None of the sufficiently large subgroups showed an inconsistent effect in this regard. Just as in the DAWNA-1 study, both premenopausal and postmenopausal women were recruited. However, in the presentation of the DAWNA-2 study investigating aromatase inhibitors as endocrine therapy, it was not specified whether or not the premenopausal women received ovarian function suppression [22]. There was no difference in the reported therapeutic effects for premenopausal patients (HR = 0.53; 95 % CI: 0.33–0.85) compared to postmenopausal patients (HR = 0.52; 95 % CI: 0.36–0.75) [22]. In terms of side effects, hematological effects such as neutropenia (grade 4: 21.2 %) were most prominent. As previously mentioned, dalpicilib has not yet been approved, either in Europe or the USA.

ELAINE 1

In the PADA-1 study, mutations in the estrogen receptor gene *(ESR1)* were associated with better efficacy when the treatment was switched to a combination with fulvestrant and palbociclib, compared to continued treatment with aromatase inhibitors [24]. In light of this, for patients with a somatic *ESR1* mutation *(sESR1)*, the question arises as to what is the best combination partner for treatment with a CDK4/6 inhibitor. One drug currently in trial is lasofoxifene, which has been shown in preclinical trials to have better efficacy against tumors than fulvestrant [25, 26]. This drug has now been trialed on a cohort in which an sESR1 mutation was detected during progression under treatment with aromatase inhibitors and CDK4/6 inhibitors. Given the small sample size of just 103 randomized patients, the hazard ratio at 0.699 (95 % CI: 0.445–1.125; p = 0.138) was not statistically significant; nevertheless, it was highly promising. The median PFS in this therapy-resistant context was increased from 4.04 months to 6.04 months [27].

MSK-Impact

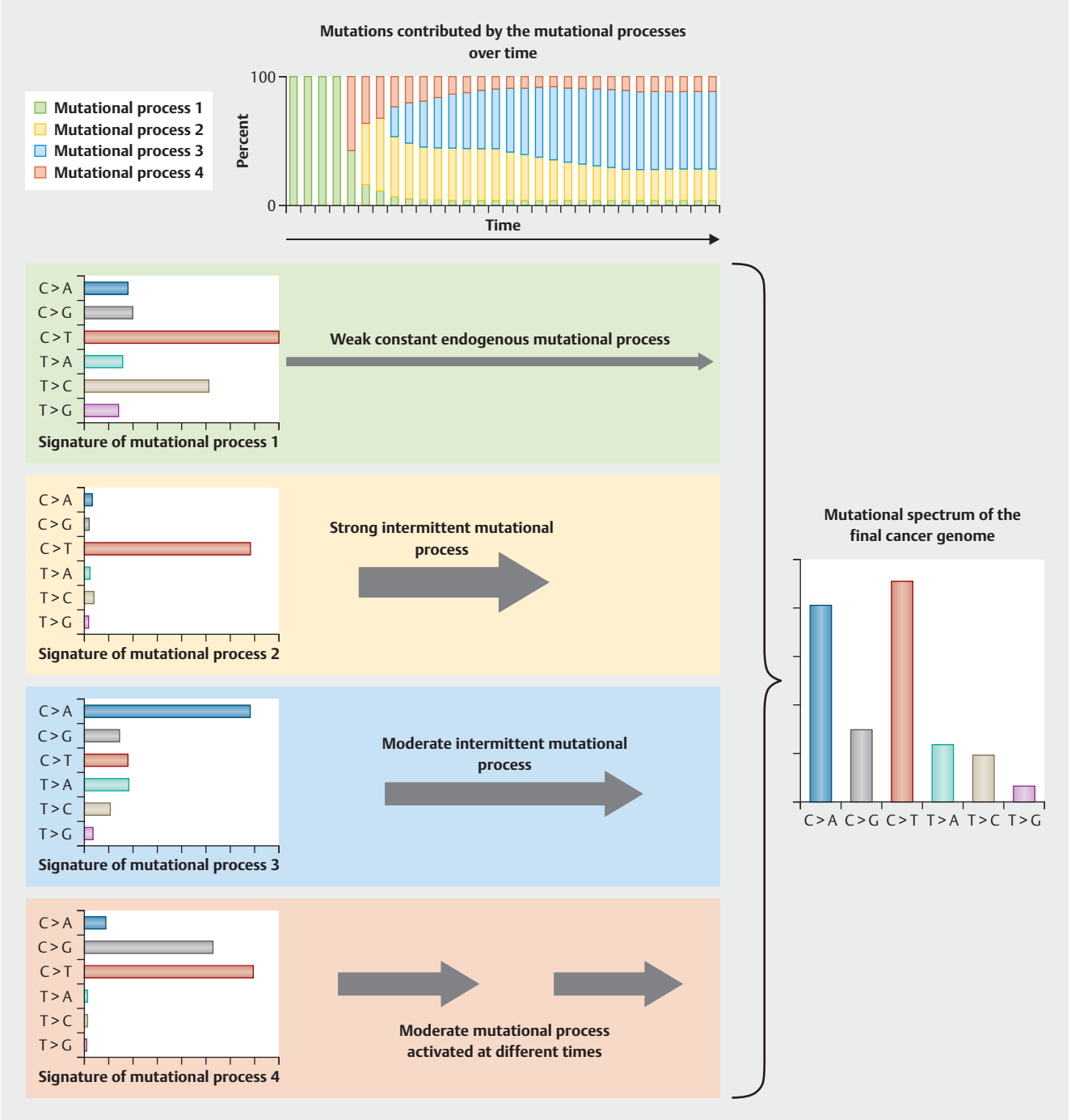
Data from the MSK-IMPACT cohort relating to the prognosis for patients treated with CDK4/6 inhibitors have already been presented at the 2021 San Antonio Breast Cancer Symposium. At this conference, data were presented showing that a germline mutation in *BRCA2* had an unfavorable effect on the prognosis for patients treated with a CDK4/6 inhibitor. Compared to patients with the wild-type genotype, patients with a mutation had a higher risk of progression (HR = 2.32; 95 % CI: 1.38–3.91) [28].

We are now being presented with new, extensive biomarker analyses for this cohort, again in relation to patients treated with CDK4/6 inhibitors [29]. For this purpose, the tumors of breast cancer patients were studied for complex mutational signatures. The classification of tumors according to complex mutational signatures is an attempt to categorize the tumors based on their somatic mutation patterns. In the pathogenesis of tumors, different stimuli and circumstances can lead to mutations, all of which have a characteristic mutational profile [30]. An example of the development of this kind of mutational profile is set out in ▶ **Fig. 1**. These mutational profiles can be developed for different types of mutations (single base pair, doublet base pair, and INDELs). The study of the MSK-Impact cohort focused on single base substitution (SBS) mutations [29], for which 96 different mutation classes have been described in a recently published article [31]. Current classifications of tumor genomes are available in COSMIC (Catalogue of Somatic Mutations in Cancer) [32].

Some of these SBS signatures occur frequently in breast carcinomas, and can be classified according to the following etiological groups: clock-like, APOBEC, HRD, smoking, and mismatch repair deficiency. An overview is provided in ▶ **Table 1**.

The clinical data that have been presented relate firstly to a change in the mutational profile from primary tumor to metastasis, and secondly to the influence of the mutational profiles on the prognosis for patients receiving CDK4/6 inhibitors as first-line therapy. The two mutational profiles which increased the most during progression from early-stage HRpos/HER2neg disease to advanced-stage disease were APOBEC and HRD [29]. The research on mutational profiles in relation to their influence on the prognosis under first-line therapy with CDK4/6 inhibitors revealed clear differences. In patients with few mutations, the median progression-free survival was 17.8 months, compared to 12.3 months in patients with an APOBEC signature. In patients in whom an HRD signature could be identified, the median PFS was only 7.6 months (▶ **Table 2**) [29].

This study also shed light on other relevant aspects of endocrine resistance. The extent to which these insights can be used to determine therapies or treatment sequences remains to be investigated in future studies. To date, treatment with a CDK4/6 inhibitor remains the standard first-line therapy for patients with advanced HRpos/HER2neg breast carcinoma. Given the short median PFS in patients with an HRD mutational profile, the question may arise as to whether this patient group would be better off treated with a PARP inhibitor. Making up 10.5 % of CDK4/6 patients in the MSK-IMPACT cohort, this HRD group only represents a small proportion of patients; a specific study would therefore have to be conducted, or information gleaned from real world data, in order to gain further insights into this issue.



▶ **Fig. 1** Model example of the development of mutational profiles (data from [30], creative commons license CC BY, https://creativecommons.org/licenses/by/3.0/). Every stimulus leads to specific mutations of differing frequencies. Over a lifetime, different stimuli, either individually or in combination, give rise to a typical mutational profile. In the example given below, there are four mutational profiles which determine the pattern that can be found in tumors. Initially, the mutational patterns that arise through ongoing effects such as aging (mutation process 1) are predominant, then subsequently the effects of other mutation processes take over: first mutation process 4, then process 2, then process 3.

CAPTOR and MINERVA

Two studies that will help to contribute data in this context are the CAPTOR and MINERVA studies [33, 34].

The MINERVA study [34] is investigating the efficacy of abemaciclib in patients with advanced HRpos/HER2neg breast carcinoma. As part of the study, biomaterial specimens may be collected for translational research programs, in particular circulating tumor DNA (ctDNA) and germline DNA. In addition, quality of life data are being recorded electronically using the health software application CANKADO. The study design is set out in ▶ **Fig. 2**.

▶ **Table 1** Mutational profiles grouped according to etiology, based on single base substitutions (SBS) analyzed in the MSK-IMPACT cohort (data from [29]).

Etiological group	SBS groups	Description	Clinical implications
Clock-like	SBS1, SBS5	With increasing age, these mutational profiles occur equally in both normal cells and neoplastic cells.	None yet
APOBEC	SBS2, SBS13	Mutational patterns that can be induced by proteins of the AID/APOBEC family. AID/APOBEC proteins can cause mutations in DNA and RNA, and APOBEC3A is probably responsible for the majority of mutations in cancer cells.	None yet
Homologous recombination deficiency (HRD)	SBS3, SBS8	This mutational pattern results from defects in the homologous recombination genes, primarily mutations in BRCA1 and BRCA2, or methylation of the BRCA1 promotor.	PARP inhibitors, platinum-based chemotherapy
Smoking	SBS4	Mutational profile associated with smoking, e.g., as a consequence of exposure to benzopyrene.	None
Mismatch repair deficiency	SBS6, SBS15, SBS20, SBS26	These mutational profiles are found in tumors with microsatellite instability.	Immune checkpoint inhibition

▶ **Table 2** Progression-free survival in the MSK-Impact cohort receiving first-line therapy with a CDK4/6 inhibitor, grouped according to mutational profiles (data from [29]).

Group	Median PFS (95% CI)	HR (95% CI)	p-value
Less than five mutations	17.8 (15.3–25.7)	1 (reference)	
Clock-like and others	14.5 (11.0–21.0)	1.23 (0.9–1.7)	0.185
APOBEC	12.3 (8.8–14.9)	1.47 (1.1–1.9)	0.012
HRD	7.6 (5.3–12.3)	1.71 (1.2–2.5)	0.006

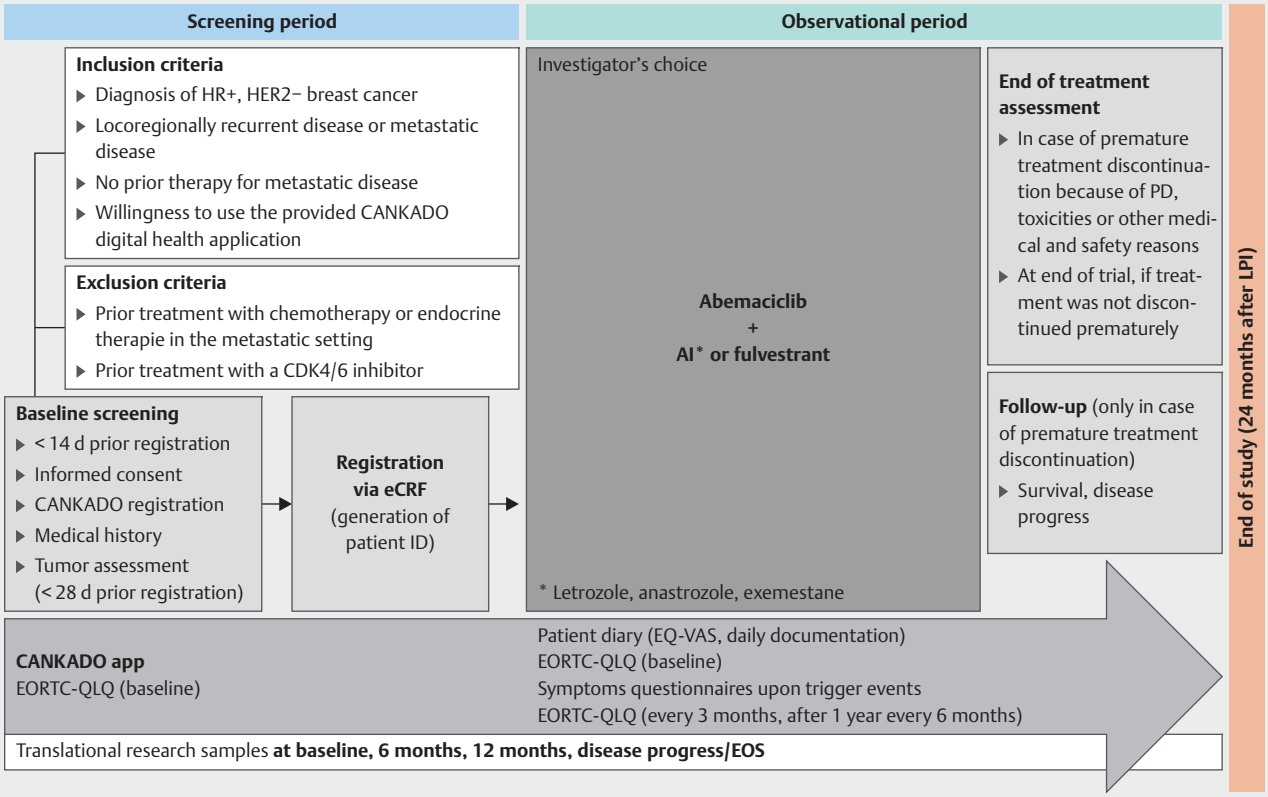
In the CAPTOR-BC study, the main focus is on investigating efficacy and resistance mechanisms using the latest methods. The visit timepoints have been optimized so as to gain extensive insights into the mechanism of action of ribociclib. For this purpose, efforts are being made to study different biomaterials: ctDNA, germline DNA, tumor tissue, serum, plasma, and leukocyte RNA. In addition, imaging data are to be associated with the efficacy of ribociclib. The study design is set out in ▶ **Fig. 3**. As shown by the mutational profiles in the MSK-IMPACT cohort, it is often necessary to study thousands of genes and mutations. For this reason, a very large sample size of patients is needed in order to investigate aspects of resistance and efficacy. The CAPTOR-BC study network is specifically prepared to share algorithms and data with other research groups; this increases the chances of achieving substantial research.

Hormone-Positive Disease and SERDs

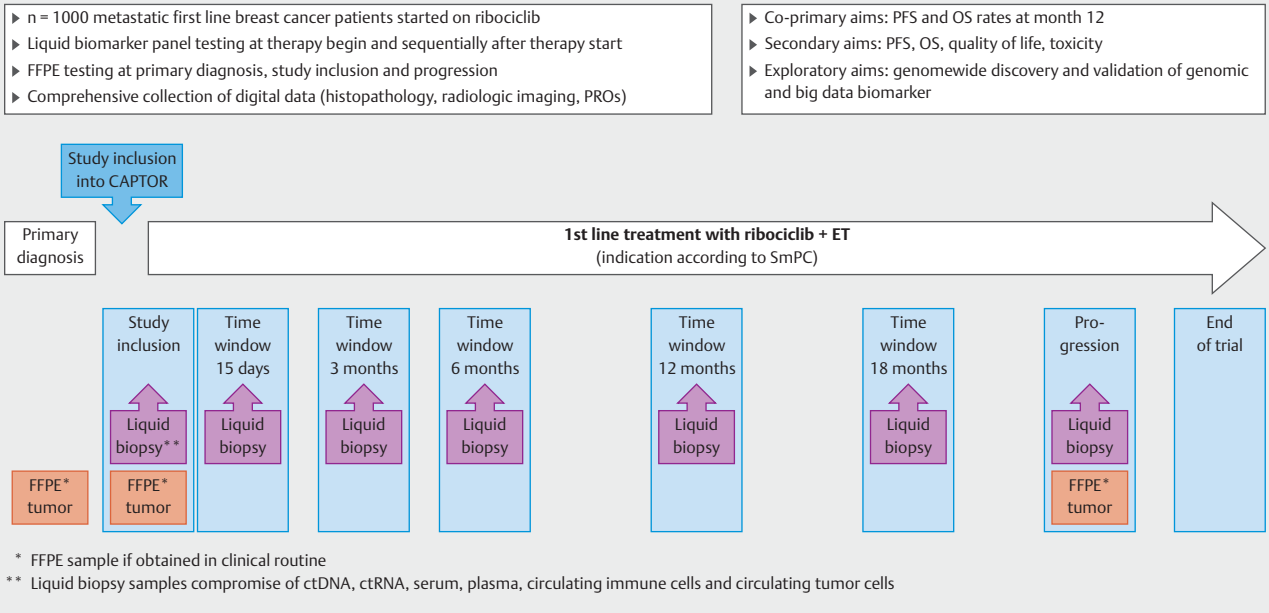
The new oral selective estrogen degraders (SERDs) are currently under clinical development. They are being trialed in a large number of clinical studies, in a wide variety of clinical settings. Two randomized studies have now reached their primary study goal: the EMERALD study and the SERENA-2 study. While the EMERALD study has already been published in full [35], so far only a press release is available for the SERENA-2 study [36]. Despite these two studies, the value of oral SERDS in treating HRpos/HER2neg breast cancer patients has yet to be established. The improvement to median PFS in the EMERALD study was only of marginal clinical significance. The median progression-free survival increased from 1.9 months to 2.8 months for the total cohort [35]. In addition, two similar studies which failed to reach their primary study goal have now been published: the acelERA study and the AMEERA-3 study [37, 38].

acelERA

The acelERA study recruited patients who had previously undergone either one or two systemic treatments for advanced-stage HRpos/HER2neg breast carcinoma. One of the treatments in this context had to be an endocrine therapy. The 303 patients were randomized to receive either monotherapy of the physician's choice (aromatase inhibitor [IA] or fulvestrant [FUL]), or therapy with giredestrant). In the comparator arm, 75% of patients were treated with fulvestrant and 25% with aromatase inhibitors. An analysis of the total cohort did not reveal any difference in terms of progression-free survival. The median PFS in the group of patients receiving giredestrant was 5.6 months, compared to 5.4 months in the FUL/AI group. This corresponded to a hazard ratio of 0.81 (95% CI: 0.60–1.10) [38]. An *ESR1* mutation was detected in a total of 90 patients. Among these patients, there was a greater difference in favor of giredestrant with an HR of 0.60 (95% CI: 0.35–1.03), with median PFS times of 5.3 months for gir-



▶ **Fig. 2** Design of the MINERVA study (AI: aromatase inhibitor, HR: hormone receptor, eCRF: electronic case report form, PD: progressive disease, LIP: last patient in, EORTC-QLQ and EQ-VAS: quality of life questionnaires, EOS: End of Study).



▶ **Fig. 3** Design of the CAPTOR-BC study.

edestrant and 3.5 months for the patients treated with FUL/AI [38].

Ameera-3

Patients in the Ameera-3 study had to have shown progression while receiving endocrine therapy in the adjuvant setting or as metastatic treatment, and were allowed to have received up to two endocrine therapies and up to one chemotherapy for the treatment of advanced-stage disease. The 290 patients in this study were randomized to receive either treatment with fulvestrant, aromatase inhibitors, or tamoxifen (TAM), or treatment with amcenestrant. In the comparator arm, 89.8% of the patients received fulvestrant, 6.8% received aromatase inhibitors, and 3.4% received tamoxifen. Again in this study, with an HR of 1.05 (95% CI: 0.79–1.4), no difference in progression-free survival could be seen for the total cohort. The median PFS times were 3.6 months for amcenestrant and 3.7 months for FUL/AI/TAM. Similarly in the Ameera-3 study, an analysis was performed of the subgroup containing 120 patients with an *ESR1* mutation. In this case, the HR was in favor of amcenestrant at 0.9 (95% CI: 0.57–1.44).

Outlook for the SERD studies

Two positive and two negative studies have now been published, including the Serena-2 study. All of these studies were conducted in a therapeutic scenario with a large number of hormone therapy-resistant patients. In populations of this kind, it is generally difficult to find evidence of a therapeutic benefit. Also, the proportion of patients in the comparator arms who received the SERD fulvestrant was relatively high. In the Ameera-3 study, this proportion was 90%. Accordingly, it can be assumed that in this study, a SERD is in fact being compared to another SERD. In August, a press release was issued announcing that the Ameera-5 study had to be discontinued. In the Ameera-5 study, first-line therapy with palbociclib plus letrozole was compared to therapy with palbociclib plus amcenestrant. The study was discontinued following an assessment by the Data Safety Monitoring Board [39]. In light of the PARSIFAL study, these results did not come as a complete surprise [40].

It is currently unclear whether the different results for these studies were due to efficacy or to the selection of the patient cohort. Even if oral SERDs can be presumed to have similar efficacy to that of fulvestrant, one of the major areas of potential is that these drugs could also be developed in the adjuvant setting. Some studies in this context have begun in the form of the lidERA study, the EMBER-4 study, and the CAMBRIA-1 study. Apart from one study, which was discontinued due to a lack of resources, fulvestrant has not yet been investigated in the adjuvant setting [41].

Hormone-Positive Disease, ADCs and Chemotherapy

TROPiCs-02

Results of the TROPiCs-02 study on the anti-Trop2 antibody–drug conjugate sacituzumab govitecan have already been presented at the 2022 ASCO Annual Meeting. The TROPiCS-02 study included HR-positive, HER2-negative patients who had to have completed several preliminary therapies. These included at least endocrine therapy, taxane therapy, and therapy with a CDK4/6 inhibitor. Study participants had to have completed at least two and no more than four chemotherapy lines for metastatic disease. Thus, only HR-positive/HER2-negative patients who had clearly completed preliminary therapies were included in this study [42].

Patients were randomized 1 : 1 to receive either treatment with sacituzumab govitecan or chemotherapy of the physician's choice (capecitabine, vinorelbine, gemcitabine, eribulin). The aim of studies of this kind should be to improve efficacy while providing a more favorable side effect profile.

Initial results showed an improvement in PFS; however, the difference in overall survival was not statistically significant. Shortly after the publication of these results, another interim analysis has now been presented [43].

While the first analysis of overall survival was based on 293 deaths, this second interim analysis was able to draw on a sample of 390 deaths [43]. Median overall survival was increased from 11.2 months (95% CI: 10.1–12.7) under chemotherapy to 14.4 months (95% CI: 13.0–15.7) under treatment with sacituzumab govitecan. This corresponded to an HR of 0.79 (95% CI: 0.65–0.96; p = 0.020). This improvement was statistically significant [43].

As a result, just a short time after the advent of CDK4/6 inhibitors and T-DXd, another study of patients with advanced HRpos/HER2neg breast carcinoma was published which shows a benefit for overall survival in this patient group.

Meteora II

Even though chemotherapy is not the treatment of choice in patients with advanced HRpos/HER2neg breast carcinoma, it is often used as a treatment option in subsequent therapy lines [45], especially following first-line therapy with CDK4/6 inhibitors [44]. However, many of these therapies are characterized by short median progression-free survival times [46,47]. It is suspected that some of the chemotherapy regimens, e.g., metronomic therapies, may also have immunomodulatory effects [48,49]. In light of this, studies comparing these kinds of chemotherapy regimens in HRpos/HER2neg patients are still useful and clinically relevant.

The recently presented METEORA-II study included patients who had received no more than one chemotherapy and no more than two endocrine therapies for the treatment of advanced HRpos/HER2neg disease [50]. The 140 patients in this study were randomized to receive either weekly paclitaxel, or a metronomic therapy with vinorelbine (days 1, 3, and 5), cyclophosphamide (oral, daily), and capecitabine (daily). Median progression-free survival in the paclitaxel arm was 6.9 months; in the arm receiving metronomic therapy, this was increased to 11.1 months (HR = 0.67; 95% CI: 0.46–0.96). There were no differences in terms of overall survival [50].

Studies like the METEORA-II study show that the chemotherapy regimens which remain popular as subsequent therapy lines can yield clear differences in terms of efficacy. One study conducted by the AGO-B in this context is the AIRE study [51], which

is investigating the immunomodulatory effect of eribulin compared to chemotherapy of the physician's choice in HER2-negative patients with advanced-stage breast carcinoma.

Interesting Research Data on Combination Therapies in HER2-Positive Patients

PHILA study

Some mechanisms involved in the treatment of patients with HER2-positive breast carcinoma have been described in connection with causes of resistance [52]. In some of these studies, the particular focus was on mutations in the PI3K signaling pathway [53–55]. The presence or accumulation of activating PI3K mutations was postulated to be a basis for some of the HER2 resistance. In light of this, the question arises as to whether the addition of a PI3K inhibitor could improve the prognosis for patients with HER2-positive disease. This question was pursued in the PHILA study [56].

Patients with metastatic disease who had not yet received treatment in this context were randomized to receive either treatment with trastuzumab and docetaxel, or treatment with trastuzumab, docetaxel, and pyrotinib. Pyrotinib is an oral, bioavailable, irreversible pan-HER-receptor tyrosine kinase inhibitor. Median progression-free survival was increased from 10.4 months to 24.3 months. This corresponded to a hazard ratio of 0.41 (95% CI: 0.32–0.53) [56].

Even though these results seem impressive, the standard first-line therapy is currently a combination of trastuzumab, pertuzumab, and chemotherapy, in accordance with data from the CLEOPATRA study [57, 58]. In this study, the median progression-free survival was increased from 12.4 months to 18.5 months. Based on these data, in addition to therapy with monoclonal antibodies, the inhibition of the PI3K signaling pathway by a targeted molecule would certainly be an interesting approach to pursue in future studies, so as to test the ability of targeted therapies to overcome resistance.

MonarchHER

In recent years, there has been significant progress in the treatment of HER2-positive breast carcinoma, with the advent of new drugs such as pertuzumab, trastuzumab emtansine (T-DM1), margetuximab, neratinib, tucatinib, and T-DXd [16, 59–62]. Except for neratinib, all of these therapies either contain or are combined with a chemotherapy. One study which gives insights into the chemotherapy-free treatment regimen is the MonarchHER study [63]. This study included patients with HRpos/HER2pos, advanced breast carcinoma, randomized into three therapy arms:

- Abemaciclib + trastuzumab + fulvestrant,
- Abemaciclib + trastuzumab,
- Chemotherapy + trastuzumab.

The final overall survival data have now been published [63]. Out of a total of 237 randomized patients, a total of 157 deaths were recorded. No statistically significant differences were found, although the chemotherapy arm had the numerically lowest overall survival at 20.7 months, and the abemaciclib + trastuzumab + fulvestrant arm had the longest median overall survival at 31.1 months (HR = 0.71; 95% CI: 0.48–1.05; p = 0.086) [63].

With these results, it has become clear that a confirmatory study should test the hypothesis of whether or not a therapy regimen in which chemotherapy is replaced by a CDK4/6 inhibitor results in an advantage for survival. In this context, the data from the DETECT-V study are of interest; this study pursued a similar line of inquiry, looking at the combination ribociclib/endocrine therapy/trastuzumab/pertuzumab. Initial data were presented at the 2022 San Antonio Breast Cancer Symposium.

Outlook

With the ongoing development of endocrine therapy options and insights into molecular mechanisms that are associated with efficacy and resistance in endocrine-based therapies, the focus is shifted increasingly towards the question of individual biomarkers for special therapy sequences. In this context, finding the best combination partner for the CDK4/6 inhibitors is just as important as the question of which subsequent therapies should be used, e.g., chemotherapy, T-DXd, or sacitzumab govitecan, and in which sequence. Especially given the insights into HRD mechanisms that can lead to endocrine resistance, PARP inhibitors have once again become a focus in the treatment of HRpos/HER2neg patients. For HER2-positive patients, there are numerous studies, either currently active or in the evaluation phase, investigating the value of the new antibody–drug conjugates. In this context, data from future studies investigating T-DXd in earlier therapy settings may once again change the therapeutic landscape.

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