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Update Breast Cancer 2024 Part 3 – Patients with Advanced Stage Breast Cancer

Update Mammakarzinom 2024 Teil 3 – Patientinnen mit fortgeschrittenen Stadien des Mammakarzinoms

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ABSTRACT

The use of CDK4/6 inhibitors, the new PI3K/AKT-kinase inhibitors, selective estrogen receptor-degraders (SERDs), antibody-drug conjugates, immune therapies and PARP inhibitors in recent years has resulted in a marked change in the therapy landscape for patients with advanced stage breast cancer. CDK4/6 inhibitors, trastuzumab deruxtecan, and sacituzumab govitecan have all been shown to provide significant overall survival benefits compared to conventional chemotherapy. Other substances are also showing promising results and hold out the hope that further analysis of the overall survival benefits will be available in the near future. The speed at which studies are now being carried out has markedly increased, and conferences and specialist journals are now constant sources of new information. This review summarizes the most recent publications and conference presentations on the treatment of patients with advanced stage breast cancer.

ZUSAMMENFASSUNG

Mit den CDK4/6-Inhibitoren, den neuen PI3K/AKT-Kinase-Inhibitoren, den selektiven Östrogenrezeptor-Degradern (SERDs), den Antikörper-Wirkstoff-Konjugaten, den Immuntherapien und den PARP-Inhibitoren wurde die Therapielandschaft von Patientinnen mit fortgeschrittenem Mammakarzinom in den letzten Jahren deutlich zum Positiven verändert. CDK4/6-Inhibitoren, Trastuzumab-Deruxtecan und Sacituzumab-Govitecan haben zudem alle einen signifikanten Gesamtüberlebensvorteil gegenüber konventioneller Chemotherapie nachgewiesen. Weitere Substanzen zeigen ebenfalls vielversprechende Daten, die hoffen lassen, dass in naher Zukunft weitere Analysen mit einem Gesamtüberlebensvorteil vorliegen. Die Geschwindigkeit der Studiendurchführung hat deutlich zugenommen, sodass die Kongresse zusammen mit den Fachzeitschriften eine stetige Quelle neuer Informationen bieten. Diese Übersichtsarbeit fasst die jüngsten Veröffentlichungen und Kongresspräsentationen über die Behandlung von Patientinnen mit fortgeschrittenen Stadien einer Mammakarzinomerkrankung zusammen.

Tumor Genetics: New Confirmatory Data on Olaparib and PALB2 Mutations

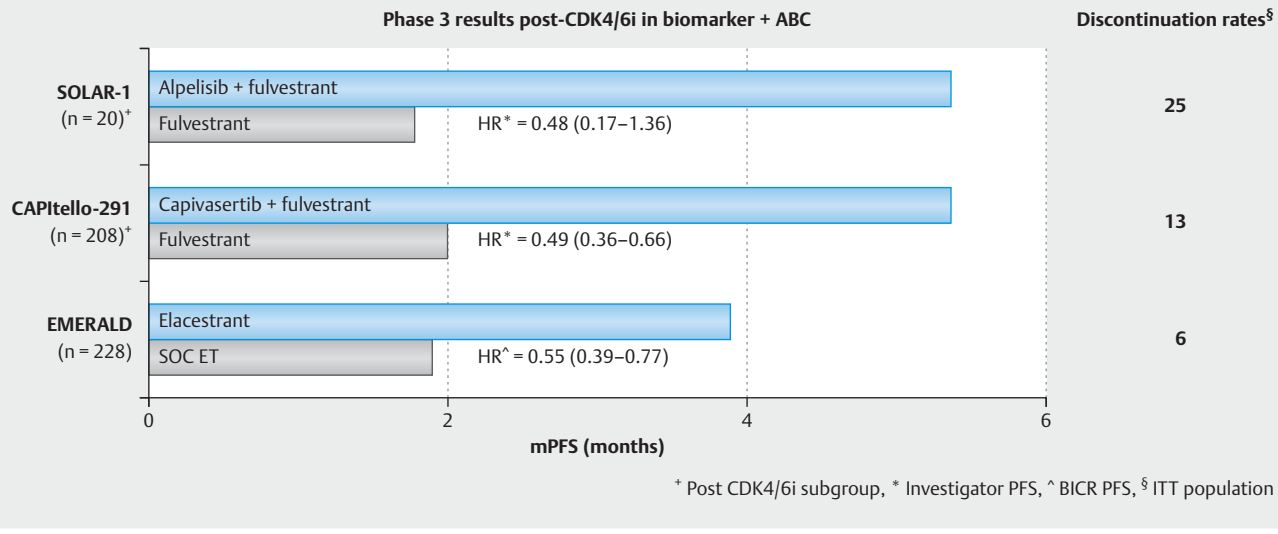
The PARP inhibitors olaparib and talazoparib have been approved to treat patients with germline mutations in *BRCA1/2 (gBRCA1/2)* and advanced triple-negative breast cancer (TNBC) or hormone receptor-positive/HER2-negative (HRpos/HER2neg) breast cancer [1–4]. Even though the approval studies did not show a significant overall survival benefit [5], the rationale for approving these alternative therapy options in the respective therapy situation was the increase in progression-free survival (PFS) and the clear improvement in quality of life [1,6] compared to chemotherapy [7].

Given these successes, the question naturally arises whether these agents could also be effective when defects are present in other homologous recombination or somatic *BRCA1/2* mutations. The TBCRC048 trial investigated this question [8]. Out of a total of 11 patients with germline *PALB2* mutations, 9 (82%) showed an objective response [8]. In the group of patients with somatic *BRCA1/2* mutations, an objective response was observed in 50% of cases (8 of 16 patients) [8].

The number of patients in these two groups (*gPALB2* and *sBRCA1/2* mutations) has now been increased [9]. A total of 24 patients with *gPALB2* mutation were recruited, 18 of whom (75%) showed an objective response [9]. The median PFS was 9.6 months (90% confidence interval [CI]: 8.3–12.4).

A total of 30 patients with *sBRCA1/2* mutation were recruited. Of these patients, 11 (36%) showed an objective response. The median PFS was 7.2 months (90% CI: 3.9–13.6).

It should be noted that the majority of patients in the expanded cohort had hormone receptor-positive tumors (77% and 79%). A subgroup analysis was carried out for the total group of



▶ **Fig. 1** Study results for endocrine therapy options after first-line therapy with a CDK4/6 inhibitor (Fig. based on data from: [18–20, 24]) (ABC: advanced breast cancer; mPFS: median progression-free survival; HR: hazard ratio; CDK4/6i: CDK4/6 inhibitor; BICR PFS: progression-free survival assessed by blinded independent central review; ET: endocrine therapy; ITT: intention-to-treat).

patients with *sBRCA1/2* mutated tumors from both recruitment phases (n = 65). The overall response rate (ORR) was higher for TNBC (ORR: 70%) compared to HRpos/HER2neg (ORR: 36%). Similarly, a better response rate of 71% was observed for the first line of therapy, compared with 24% in patients in receiving other advanced therapy lines [9].

This means that the results of the first study [8] have been confirmed. Overall, higher anti-tumor activity appears to be present in patients with a *gPALB2* mutation. This makes olaparib a valid therapy option in cases where alternative options are lacking. In practice, this is more rarely the case for patients with TNBC compared to patients with HRpos/HER2neg disease, because there are now a number of established therapies which offer an overall survival benefit (ribociclib, abemaciclib, trastuzumab deruxtecan, sacituzumab govitecan and, if needed, capivasertib) and an appropriate therapy with olaparib is therefore usually considered in later therapy lines. But *PALB2* mutations are rare (only around 1.1% of all patients with metastatic breast cancer) [10]. The mutation frequency in patients with TNBC is 1.2%; it is 0.9% for luminal A-like subtype and 3.2% for luminal B-like breast cancer [10].

Efficacy and Quality of Life as Cornerstones in the Treatment of Patients with HRpos/HER2neg Breast Cancer

More data on "treatment beyond progression" after CDK4/6 inhibitors

The standard approach used for the first-line treatment of patients with advanced HRpos/HER2neg breast cancer consists of CDK4/6 inhibitors combined with endocrine therapy. After the publication of the results of ribociclib trials (MONALEESA-2, -3 and -7) which showed a significant survival benefit [11–13] and the clear trend towards an overall survival benefit demonstrated in the MONARCH 3 trial for abemaciclib (hazard ratio for overall survival [OS]: 0.804; 95% CI: 0.637–1.015; p = 0.066) [14], the majority of patients in this setting are given a CDK4/6 inhibitor [15, 16]. But the question often arises which therapy should be administered following therapy with a CDK4/6 inhibitor. In clinical practice, some patients are treated with everolimus and endocrine therapy, although the efficacy data for this therapy sequence is limited, especially after prior therapy with a CDK4/6 inhibitor [17]. This therapeutic situation has been investigated in randomized studies such as the EMERALD trial [18] with elacestrant and the CAPitello-291 study of capivasertib combined with fulvestrant [19]. The Solar-1 study also had a small group of patients who were included in the study after prior therapy with a CDK4/6 inhibitor and treated with alpelisib [20] (▶ **Fig. 1**). For patients who received an aromatase inhibitor combined with a CDK4/6 inihibitor as their first-line therapy, another option currently under discussion is to continue with CDK4/6 inhibitor therapy even after progression and switch the endocrine combination partner (therapy beyond progression). However, because the results to date have been inconsistent and the number of patients studied up to now is small, the Consensus Panel of the ABC7 Conference were unable to bring themselves to issue a recommendation for this approach [21–23]. The primary outcomes of the postMONARCH trial which addressed this issue have now been published [24]. ▶ **Table 1** provides an overview of the studies carried out in this therapeutic setting: MAINTAIN, PALMIRA, PACE and postMONARCH [24–27].

The postMONARCH trial included patients who had been treated with palbociclib or ribociclib and an aromatase inhibitor as the first advanced therapy line. The 368 patients were randomized ei-

▶ **Table 1** Overview of CDK4/6 trials in "treatment beyond progression" settings (data from: [24–27]) (CDK4/6i: CDK4/6 inhibitor; ET: endocrine therapy).

	postMONARCH	MAINTAIN	PALMIRA	PACE
Phase	3	2	2	2
Number of patients	368	132	198	220
Prior chemotherapy	0%	9%	0%	16%
Prior palbociclib	60%	85%	100%	91%
Prior ribociclib	33%	12%	0%	4.5%
Prior abemaciclib	8%	2%	0%	4.1%
Second-line	100%	65%	100%	77%
> second-line	0%	18.5%	0%	17%
CDK4/6i on trial	Abemaciclib	Ribociclib	Palbociclib	Palbociclib
ET on trial	Fulvestrant	Fulvestrant or exemestane	Letrozole or fulvestrant	Fulvestrant

ther into one arm with fulvestrant monotherapy or a second arm where therapy consisted of fulvestrant and abemaciclib. The combination therapy resulted in a statistically significantly longer median PFS (6.0 months vs. 5.3 months, hazard ratio = 0.73; 95% CI: 0.57–0.95) [24]. This effect was consistent across the subgroup analyses. It appeared that the therapy had a slightly better hazard ratio in patients without visceral metastases (hazard ratio = 0.53; 95% CI: 0.34–0.83) compared to patients with visceral metastases (hazard ratio = 0.87; 95% CI: 0.64–1.17). The interaction test had a p value of 0.07 [24]. Even the presence of *ESR1* mutations or *PIK3CA*/*AKT*/*PTEN* alterations had no effect on the different efficacy levels [24].

The postMONARCH trial could therefore give fresh impetus to the "therapy beyond progression" option as this therapy could have a more favorable side-effects profile compared with other targeted options such as everolimus, alpelisib, and capivasertib.

Interestingly, the postMONARCH study was originally designed so that patients who had previously been treated with CDK4/6 inhibitors in the adjuvant setting could also be included [24]. These patients would have provided valuable information about the behavior of patients who develop metastasis after adjuvant treatment with a CDK4/6 inhibitor. There are currently no data which suggest a standard approach for the first-line therapy of patients with metastasis. But unfortunately only two such patients were included in the postMONARCH trial.

New combination therapies for the first HRpos/HER2neg therapy line – new data on PIK3CA inhibition

Although CDK4/6 inhibitors are a standard part of first-line therapy and extend OS, the majority of patients experience progression after a median of 2 years and still die from breast cancer. More and more patients receiving adjuvant treatment will receive a CDK4/6 inhibitor in the coming years. The study data on metastasis is limited and the postMONARCH trial has not provided any data in this setting. Research should therefore prioritize getting a better understanding of the primary and secondary resistance mechanisms of CDK4/6 inhibitor therapy and the options to increase effectiveness.

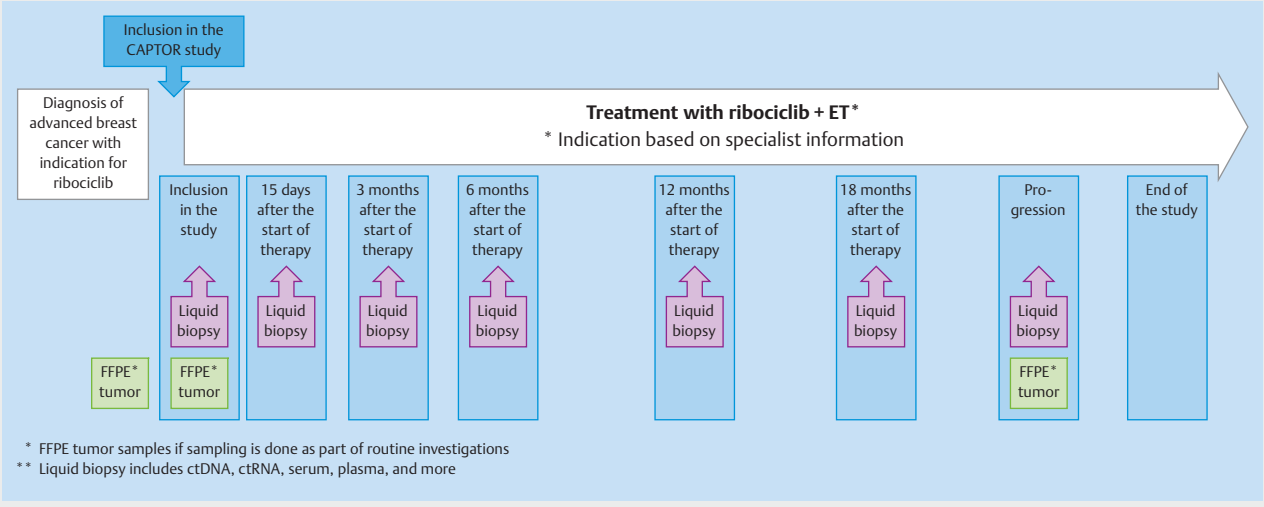
The CAPTOR study is a research program in Germany which is focusing on the discovery and validation of biomarkers which can predict the effectiveness of and resistance to ribociclib [28] (▶ **Fig. 2**). Large numbers of patients will be necessary to detect stable patterns to characterize the effectiveness of ribociclib. The first indications were provided in the PALOMA-3 study [29, 30]. Circulating tumor DNA (ctDNA) samples were used to compare genomic changes prior to therapy and after progression. Mutations in the *ESR1* and *PIK3CA* genes were found more often at the end of therapy than at the start [30]. Similar investigations were also carried out in the MONARCH-2 trial. However, the investigated *ESR1* and *PIK3C* mutations had no effect on prognosis [31]. Similar extensive analysis was carried out in ribociclib studies (MONALEESA-2, -3 and -7) which included more than 1700 patients [32]. Out of 550 investigated genes, the most common mutation was a *PIK3CA* mutation (33%).

This makes the INAVO120 study especially interesting. The INAVO120 study also included patients who received first-line advanced therapy but showed some signs of endocrine resistance as evidenced by progression under therapy or within 12 months after the end of adjuvant endocrine therapy. A *PIK3CA* gene mutation was required for inclusion. The 325 patients were randomized to receive either therapy consisting of palbociclib + fulvestrant or therapy with palbociclib + fulvestrant + inavolisib [33]. The PFS in the comparative arm was 7.3 months, which indicates an endocrine-resistant population. The addition of inavolisib was able to extend the median PFS to 15 months (hazard ratio = 0.43; 95% CI: 0.32–0.59; p < 0.0001) [33]. Even though the difference in OS was not (yet) formally statistically significant, the difference between the two arms was promising, with a hazard ratio of 0.64 (95% CI: 0.43–0.97; p = 0.0338). It should be noted that the p value would have to be 0.0098 to achieve statistical significance. The most commonly reported side effects of this triple combination compared to the comparative arm were stomatitis (51.2% vs. 26.5%), hyperglycemia (58.6% vs. 8.6%), diarrhea (48.1% vs. 16.0%), nausea (27.8% vs. 16.7%) and rash (25.3% vs. 17.3%) [33]. Serious side effects (grade 3 and 4) tended to be rare. Just 5.6% of patients developed grade 3/4 stomatitis and 5.6% of pa-

Study design and study objectives

- N = 2000 patients with advanced breast cancer and an indication for ribociclib
- Liquid biopsy at the start of the study and sequentially over the course of the study
- FFPE tumor samples if sampling is done as part of routine investigations
- Collection of all digitally available information (histological, radiological images …)

- Co-primary study endpoints: PFS and OS rates after 12 months
- Secondary study endpoints: PFS, OS, quality of life, tolerability
- Exploratory study endpoints: genome-wide biomarker detection and validation



Germline DNA: HR genes, genome-wide SNPs

ctDNA changes over time to monitor disease

ctDNA for molecular tumor characterization

ctDNA for molecular tumor characterization

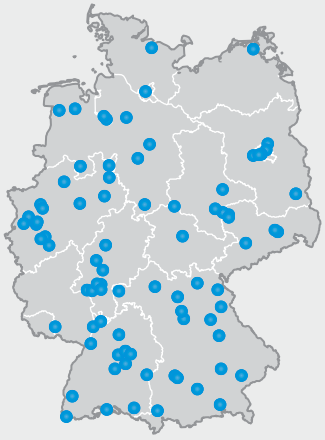
Leukocyte RNA for immunological characterization

Leukocyte RNA for immunological characterization

FFPE for spatial multiomics

FFPE for spatial multiomics

Participating centers



Involved study groups/professional associations

- AGO-B Breast Study Group
- Gynecological oncology working group (AGO)
- German Society of Senology

▶ **Fig. 2** Study design of the CAPTOR BC study and planned molecular analyses (source: Schneeweiss A, Brucker SY, Huebner H et al. CDK4/6-Inhibition: Sequenztherapien und die Suche nach den besten Biomarkern – ein Überblick über die aktuellen Programme. Geburtshilfe Frauenheilkd 2024; 84: 443–458. DOI: 10.1055/a-2286-6066. © 2024. The author[s]. License: CC BY-NC-ND 4.0 [https://creativecommons.org/licenses/by-nc-nd/4.0/]. No changes were made.) (ET: endocrine therapy; FFPE: formalin-fixed paraffin-embedded tissue; PFS: progression-free survival; OS: overall survival; SNP: single nucleotide polymorphism; ctDNA: circulating tumor DNA)

tients experienced grade 3/4 hyperglycemia [33]. Compared with 0.6% in the comparative arm, 6.2% of patients who were treated with inavolisib had to discontinue therapy because of side effects.

In view of the additional side effects, it is important to consider therapy management and quality of life. Data on these issues have also been recently published [34]. In addition to the EORTC-QLQ-C30, the standard quality-of-life questionnaire, other patient-reported outcomes were also used, such as the time to increased pain interference (using the BPI-SF questionnaire) and an "overall bother" questionnaire which recorded the degree to which patients found therapy bothersome and disruptive using a five-point scale.

When the EORTC-QLQ-C30 was administered, no differences were found in the overall score, the physical functioning score and the role functioning score [34]. According to the responses to the "overall bother" questionnaire, around 50% of patients did not report impairment from the palbociclib + fulvestrant therapy; however, this was only the case for about 25% of the patients who additionally received inavolisib. But over time, a clear numerical difference became apparent including a worsening of pain symptoms. With the double combination this occurred after a median of 18 months, whereas when inavolisib was added, this occurred after about 31 months [34].

Although the efficacy seems to be very promising, we will have to await the results on the formal statistical significance of OS. It appears, however, that for the endocrine-resistant population of the INAVO120 trial, the addition of inavolisib led to a clear prolongation of PFS. It remains to be seen how the side effects, which appeared manageable in the trial, will affect clinical practice in the real world.

New AntiBody-Drug-Conjugates (ADC) and New ADC Combination Therapies

At the moment, almost no other areas of clinical development are as active as research into the efficacy and side effects of ADCs. With trastuzumab deruxtecan and sacituzumab govitecan, two ADCs have already been approved to treat patients with advanced breast cancer. Trastuzumab deruxtecan can be used to treat HER2-positive and HER2-negative tumors with low HER2 expression (HER2-low) while sacituzumab govitecan is used to treat patients with TNBC or HRpos/HER2neg breast cancer and the appropriate indications.

Establishment of trastuzumab deruxtecan to treat HER2-low and HER2-ultralow HRpos/HER2neg patients after prior endocrine therapy – DESTINY-Breast06

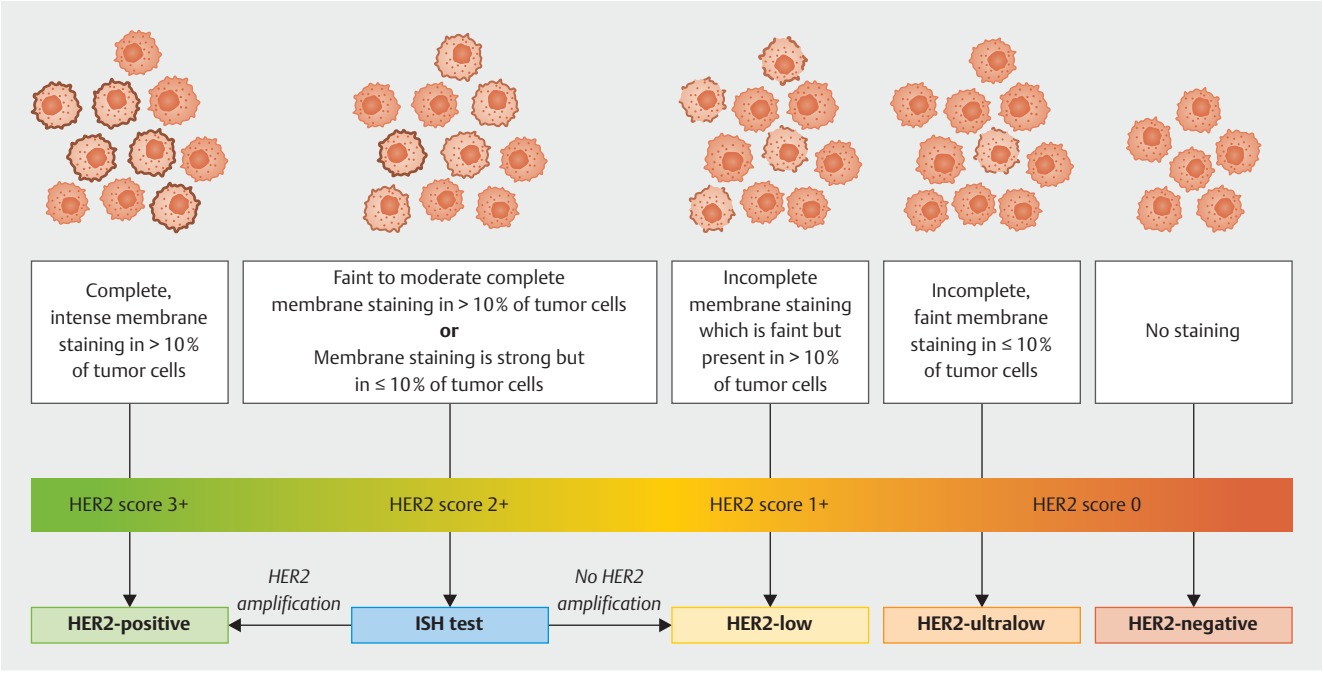
One of the insights obtained from ADC research in recent years is that many substances have a wide efficacy spectrum. Trastuzumab deruxtecan, for example, which targets HER2, was first tested in patients with HER2-positive breast cancer. The data from the DESTINY-Breast01 and the DESTINY-Breast03 trials demonstrated a high level of efficacy against this tumor entity [35, 36]. The DESTINY-Breast04 trials in HER2-negative patients with lower HER2 expression (defined as ICH 1+ und 2+ with *ERBB2* gene amplification [both HRpos/HER2neg and TNBC]) then demonstrated a clinically relevant efficacy in a population where HER2 was not the driver of disease [37]. The OS was prolonged by a median of six months in HRpos/HER2neg patients with HER2-low expression and at least one prior endocrine therapy and chemotherapy [37]. Data from the DESTINY-Breast06 trial has now been published [38]. The study also included patients with two previous endocine therapies and low or ultralow HER2 expression. HER2-low expression is defined as incomplete, faint immunohistochemical membrane staining in more than 10% of tumor cells. With HER2-ultralow expression, membrane staining is incomplete, faint and found in ≤ 10% of tumor cells [39, 40] (▶ **Fig. 3**). In addition to the patients with HER2-low expression in the group of HRpos/HER2neg patients who accounted for about 60–65% of patients, a further 20–25% of HRpos/HER2neg patients were included who had HER2-ultralow expressing tumors [38].

Patients were included in the DESTINY-Breast06 trial if they had HER2-low or ultralow expressing tumors, they were clinically HRpos/HER2neg, had not previously had chemotherapy but had had at least two previous endocrine therapy lines in the metastatic setting. Alternatively, endocrine resistance was also defined as metastasis within 24 months after the start of adjuvant endocrine therapy. Patients were randomized 1 : 1 to therapy with trastuzumab deruxtecan or therapy with capecitabine, nab-paclitaxel or paclitaxel (chemotherapy at the physician's choice; TPC). The primary endpoint was PFS in the HER2-low population. The median follow-up time for the 866 randomized patients was 18.2 months. In the HER2-low population, median PFS increased from 5.1 months in the TPC arm to 13.2 months in the trastuzumab deruxtecan arm (hazard ratio = 0.62; 0.51–0.74; $p < 0.0001$ [38]. The median PFS in the HER2-ultralow population also increased numerically from 4.9 months to 13.2 months (hazard ratio = 0.78; 95% CI: 0.50–1.21). The data on OS were considered to be not yet mature enough for publication in view of the limited observation period. The hazard ratio for OS in the HER2-low group was 0.83 (95% CI: 0.66–1.05) [38]. Fatalities due to interstitial lung disease were again observed in the study (n = 3; 0.7%). It is therefore important to carry out regular CT scans and take appropriate measures if respiratory symptoms occur when patients are receiving treatment with trastuzumab deruxtecan. Apart from that, the side-effects profile was similar to that reported in the other DESTINY-Breast studies [38].

With the approval of trastuzumab deruxtecan, data on a third-line therapy after two previous endocrine therapies is now available which is more effective than chemotherapy alone. This should lead to the increasing administration of therapy sequences which use endocrine therapy options in the first two lines of therapy, followed by the administration of trastuzumab deruxtecan as the first chemotherapy-containing option for the third-line therapy. It is possible that the standard administration of chemotherapy alone as a second-line therapy [16] will decrease. Future real-world studies will show whether this approach will be confirmed.

Moderate efficacy with the anti-Nectin-4 ADC enfortumab vedotin

The results for trastuzumab deruxtecan have not just demonstrated the efficacy of this antibody-drug conjugate across a wide



▶ **Fig. 3** Spectrum of HER2 expression used to categorize HER2-low and HER2-ultralow (source: Venetis K, Crimini E, Sajjadi E et al. HER2 Low, Ultra-low, and Novel Complementary Biomarkers: Expanding the Spectrum of HER2 Positivity in Breast Cancer. Front Mol Biosci 2022; 9: 834651. DOI: 10.3389/fmolb.2022.834651. © 2022 Venetis, Crimini, Sajjadi, Corti, Guerini-Rocco, Viale, Curigliano, Criscitiello and Fusco. Licensed under Creative Commons Attribution License [CC BY] [https://creativecommons.org/licenses/by/4.0/]. The image has been adapted.) (ISH: in situ hybridization)

spectrum of HER2 expression. The DESTINY-PanTumor studies [41,42] have also demonstrated that ADCs can be effective to treat other tumor entities as well. This is an excellent rationale to test whether ADCs which have been shown to be effective against other cancers can also be used to treat breast cancer. ▶ **Table 2** provides an overview of the ADCs currently approved by the FDA. The EV-202 study has now also provided data on one of these ADCs, enfortumab vedotin, in the context of HRpos/HER2neg breast cancer and TNBC [43]. Enfortumab vedotin is based on an anti-Nectin-4 antibody and the payload is monomethyl auristatin E. It has already been approved to treat pre-treated metastatic urothelial carcinoma.

The phase II breast cancer study included patients who were either HRpos/HER2neg and had had prior endocrine therapy with or without CDK4/6 inhibitors or patients with TNBC who required prior therapy with immune checkpoint inhibitors if they had PD-L1 expression. 45 patients with HRpos/HER2neg breast cancer and 42 patients with TNBC were included. The efficacy was moderate. The response rate of the HRpos/HER2neg group was 15.6% and the median PFS was 5.4 months (95% CI: 3.4–5.7). The response rate of the patients with TNBC was 19.0% and the median PFS was 3.5 months (95% CI: 2.1–4.6) [43]. The most commonly reported side effects which occurred in 40% of cases (all grades) were fatigue, pruritus, maculopapular rash, and nausea. These side effects were similar to those reported in other studies.

The moderate efficacy together with the reported side effects begs the question how this ADC could be integrated into the therapy landscape for breast cancer. Although in the sample Nectin-4 was highly expressed [43], this does not necessarily mean that the ADC will have the same high efficacy known to exist for trastuzumab deruxtecan and sacituzumab govitecan.

Combination of ADCs with immune therapies

Large-scale study programs have recently been launched to investigate different combinations of current ADCs with immune checkpoint inhibitors. Although the number of patients with TNBC included in the BEGONIA phase 1/2 study is small, the data on the combination of durvalumab with trastuzumab deruxtecan or datopotamab deruxtecan with durvalumab is already showing impressive results. The multi-arm BEGONIA study investigated small cohorts of patients with TNBC using the following treatments:

- Arm 1: durvalumab + paclitaxel
- Arm 2: durvalumab + paclitaxel+capivasertib
- Arm 5: durvalumab + oleclumab+paclitaxel
- Arm 6: durvalumab + trastuzumab deruxtecan (with HER2-low expression)
- Arm 7: durvalumab + datopotamab deruxtecan (irrespective of PD-L1 status)
- Arm 8: durvalumab + datopotamb deruxtecan (PD-L1 status positive)

In Arm 7, 62 patients had a response rate of 79% (95% CI: 67–88) [44], while 26 of 46 patients showed a tumor response in Arm 6 (57%; 95% CI: 41–71) [44]. This is a good rationale to pursue these combination therapies further.

▶ **Table 2** ADCs already approved in the USA with payload, antibody-drug ratio, tumor type and target.

Name	Target	Linker	Payload	Type of cancer	Drug-antibody ratio	Initial FDA/USA approval for first tumor type
Trastuzumab emtansine (T-DM1)	HER2	Non-cleavable	Maytansine (DM1)	HER2pos breast cancer	3,5	22.02.2013
Enfortumab vedotin (EV)	Nectin-4	Cleavable	Monomethyl auristatin E (MMAE)	Urothelial carcinoma	4	18.12.2019
Trastuzumab deruxtecan (T-DXd)	HER2	Cleavable	Deruxtecan	HER2pos and HER2-low-expressing breast cancer, HER2pos esophageal cancer; HER2 mutated NSC lung cancer	8	20.12.2019
Sacituzumab govitecan (SG)	TROP2	Cleavable	SN-38	Triple negative breast cancer, Urothelial carcinoma	7,6	22.04.2020
Tisotumab vedotin	Tissue factor	Cleavable	Monomethyl auristatin E (MMAE)	Cervical cancer	4	20.09.2021
Mirvetuximab soravtansine	FR	Cleavable	DM4	Ovarian cancer	3 to 4	14.09.2022

The recently published SACI-IO study included pembrolizumab and sacituzumab, two established substances [45]. The SACI-IO study was carried out to test the hypothesis that an immune therapy could support sacituzumab govitecan in the treatment of patients with HRpos/HER2neg breast cancer.

Patients were included in the SACI-IO study if they had HRpos/HER2neg advanced breast cancer and had had at least one previous endocrine therapy or experienced progression under adjuvant therapy within 12 months. Up to one previous chemotherapy was permitted but it was not a precondition for inclusion in the study. PD-L1 status played no role in the inclusion and exclusion criteria.

The 104 patients were randomized 1:1 either to the standard arm to receive sacituzumab govitecan therapy or to the experimental arm where therapy consisted of sacituzumab govitecan + pembrolizumab. The primary endpoint was PFS. The median PFS increased from 6.22 months in the sacituzumab govitecan arm to 8.12 months in the sacituzumab govitecan + pembrolizumab arm. But with a hazard ratio of 0.81 (95% CI: 0.51–1.28; p = 0.37), the difference was not significant. There was also no difference in overall survival, with a median OS of 18.0 months in the sacituzumab govitecan arm and 18.5 months in the sacituzumab govitecan + pembrolizumab arm (hazard ratio = 0.65; 95% CI: 0.33–1.28; p = 0.21) [45]. No further trends were identified in the subgroups categorized according to PD-L1 status, even though there appeared to be a slight numerical indication of efficacy in the PD-L1-positive group (CPS > 0) with a hazard ratio of 0.62 (95% CI: 0.29–1.36) compared to the CPS = 0 group which had a hazard ratio of 1.06 (95% CI: 0.59–1.90).

More results will be needed to see whether this approach should be developed further in this therapy setting. It may be necessary to first identify a patient population for whom this combination therapy is effective.

Combination therapies with trastuzumab deruxtecan in the first HER2-positive advanced therapy line

The DESTINY-Breast07 trial was designed to obtain initial insights into the efficacy and side effects of various new therapy options, using trastuzumab deruxtecan as first-line therapy for previously untreated patients with advanced HER2-positive breast cancer [46]. The following combination therapies and a comparative arm with T-DXd monotherapy are planned:

- trastuzumab deruxtecan monotherapy
- trastuzumab deruxtecan + durvalumab
- trastuzumab deruxtecan + pertuzumab
- trastuzumab deruxtecan + paclitaxel
- trastuzumab deruxtecan + durvalumab + paclitaxel
- trastuzumab deruxtecan + tucatinib
- trastuzumab deruxtecan monotherapy for patients with brain metastases (all other arms require the absence of brain metastases)

The initial data from the first HER2-positive therapy line with trastuzumab deruxtecan have been published recently. After the publication of the CLEOPATRA study [47,48], standard therapy consisted of a combination of taxane + pertuzumab + trastuzumab [7,21,22,49]. In the CLEOPATRA study, the median PFS of 12.4 months obtained with trastuzumab and docetaxel was increased to 18.7 months by the addition of pertuzumab [50]. Similarly, the median overall survival of 40.8 months increased to 57.1 months compared to trastuzumab [50]. In the still ongoing randomized DESTINY-Breast09 study, monotherapy with trastuzumab deruxtecan is compared to trastuzumab deruxtecan and pertuzumab [51]. The results of the DESTINY-Breast09 study are not yet available. However, data is available for the significantly smaller patient groups of the DESTINY-Breast07 study [52]. 75 patients were included in the trastuzumab deruxtecan

monotherapy arm und 50 previously untreated patients with advanced HER2-positive breast cancer were included in the trastuzumab deruxtecan + pertuzumab arm. The majority of patients (605) had de novo metastatic breast cancer, which roughly corresponds to the natural distribution for this tumor entity [53]. 52–65% of cases with recurrence had previously been treated with trastuzumab and 10–14.8% had additionally received pertuzumab [52]. The median observation time for the trastuzumab deruxtecan monotherapy arm was 23.9 months and the median observation time for the combination arm was 25.3 months. The median PFS was not achieved in either arm. The PFS rate for the trastuzumab deruxtecan arm was 80.8% after 12 months and 89.4% for the combination arm. By comparison, in the CLEOPATRA study this rate was approximately 67% (extracted from [50] using [54]).

This data is definitely raising expectations about the forthcoming results of the DESTINY-Breast09 study which compares these two therapies with the current standard therapy using a randomized design.

Quality of life with datopotamab deruxtecan – experience from the TROPION-Breast01 study

Most ADCs have more and new side effects compared to standard therapies, and management of these side effects is usually more complex. However, the substances are more effective. It has now also been demonstrated that progression per se has a negative impact on quality of life [55]. In this context, evaluating the benefits and risks of ADCs could be quite difficult. Datopotamab deruxtecan is an ADC which has not yet been approved but has been clinically tested. It is an ADC which, like sacituzumab govitecan, targets Trop2 but uses deruxtecan as the payload (like trastuzumab deruxtecan). The TROPION-Breast01 study has already provided evidence that PFS is better compared to chemotherapy. 732 patients with advanced HRpos/HER2neg breast cancer were randomized into the phase III study. Patients who experienced progression under endocrine therapy and who were not candidates for further endocrine therapy were included. These patients also had to have previously received one or two conventional chemotherapy lines. Patients either received chemotherapy at the physician's choice (eribulin, vinorelbin, gemcitabine or capecitabine) or datopotamab deruxtecan. Primary endpoints were PFS and OS [56]. The median PSF of 4.9 months with standard chemotherapy in this extensively treated patient population increased to 6.9 months with datopotamab deruxtecan (hazard ratio = 0.63; 95% CI: 0.52–0.76; $p < 0.0001$) [56]. The interstitial pneumonitis rate was slightly lower, with just two cases with grade 3/4 compared to trastuzumab deruxtecan. New side effects which had not previously occurred as often with other ADCs used to treat breast cancer were stomatitis and dry eyes [56].

As mentioned above, careful evaluation of quality of life is important in the context of improved efficacy and individual toxicity profiles. An evaluation of quality of life was recently published [57]. The quality-of-life analysis used the overall EORTC-QLQ-C30 questionnaire score and the pain and physical functioning subscores. Evaluation was based on time to deterioration of quality of life and time to confirmed deterioration (confirmation of ongoing deterioration at another timepoint). ▶ **Table 3** shows the hazard ratios for all analyses. All analyses showed a nominal improvement in quality of life [57].

▶ **Table 3** Comparison of quality of life using three different aspects of the EORTC-QLQ-C30 questionnaire. The HR for time to deterioraton is shown here, with chemotherapy functioning as the comparative arm. This means that values under 1 favor datopotomab deruxtecan (data from [57]).

Type of quality of life measurement	Hazard ratio	95% CI
Overall score	0.85	0.68–1.06
Overall score (confirmed)	0.76	0.58–0.98
Pain	0.85	0.68–1.07
Pain (confirmed)	0.72	0.55–0.94
Physical functioning	0.77	0.61–0.99
Physical functioning (confirmed)	0.77	0.59–1.01

These analyses show that a better quality of life can be achieved despite a potentially challenging side-effects profile. A more comprehensive assessment of these ADCs will be possible once the OS data is available as well as further data on the rate and severity of interstitial pneumonitis.

Sacituzumab tirumotecan, a new ADC with promising prospects

As the technological possibilities increase, more and more ADCs with new payloads or new antibodies are being clinically evaluated. Sacituzumab tirumotecan is a new ADC which targets Trop2 and also uses a topoisomerase I inhibitor as the payload. The drug previously produced good results in some studies with a good side-effects profile. It has now been tested in a prospective randomized phase III trial in patients with advanced TNBC [58], the OptiTROP-Breast01 study. TNBC patients with advanced breast cancer who had had at least two previous chemotherapies in the advanced setting were included. The 263 patients included in the study were randomized either to therapy with the physician's choice of chemotherapy (eribulin, vinorelbin, gemcitabine or capecitabine) or sacituzumab tirumotecan. The primary endpoint was PFS and the key secondary endpoint was OS.

PFS improved significantly from a median time of 2.3 months to 5.7 months (hazard ratio = 0.31; 95% CI: 0.22–0.45; $p < 0.00001$). This effect was independent of the extent of Trop2 expression. OS also improved significantly, with a hazard ratio of 0.53 (95% CI: 0.36–0.78; $p = 0.0005$). Specific side effects included stomatitis, rash, and elevated liver values as well as hematological toxicities. Only one patient had grade 2 interstitial pneumonitis, and dry eye was reported in another patient. With the introduction of sacituzumab tirumotecan, another anti-Trop-2 agent is now available which has been shown to prolong both PFS and OS when administered to patients mit TNBC as an advanced therapy line.

Outlook

The new inhibitors of the PI3K/Akt kinase signaling pathway, capivasertib and inavolisib, appear to be two highly effective substances, and both have the potential to offer an overall survival benefit. But it will be necessary to await the final results of the studies. Moreover, both substances require molecular testing of either the tumor or of ctDNA as a precondition for treatment, just as *ESR1* mutation testing is required for elacestrant. This could be a challenge in daily clinical practice.

Most of the new treatments for patients with advanced breast cancer are currently related to ADCs. Large study volumes and a constant stream of new substances are pushing the clinical research capacities for these patients to their limits internationally. While initial studies usually focused on testing ADC monotherapies, more and more results are now available for combination studies such as the DESTINY-Breast07 or the BEGONIA study. The first large-scale studies such as the SACI-IO trial have been concluded and published. A new generation of studies covering both advanced breast cancer treatment and treatment in the (neo)adjuvant setting will be beginning in the coming months and will focus on combination therapies, generally in combination with an immune therapy. It will be interesting to see how these two substance classes interact clinically.

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