Thieme

# Update Breast Cancer 2023 Part 2 – Advanced-Stage Breast Cancer

## Update Mammakarzinom 2023 Teil 2 – Brustkrebs in fortgeschrittenen Krankheitsstadien



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**ABSTRACT**

In recent years, a number of new therapies have led to advances in the treatment of patients with advanced breast carcinoma. These substances are mainly CDK4/6 inhibitors and other substances that can overcome endocrine resistance, oral selective estrogen receptor degraders, antibody drug conjugates (ADCs), and PARP inhibitors. This review summarizes and evaluates the latest study results that have been published in recent months. This includes the overall survival data of the Destiny-Breast03 study, the first analysis of the CAPItello-291 study, the comparison of CDK4/6 inhibitor treatment with chemotherapy in the first line of therapy (RIGHT Choice study), the first analysis of the Destiny-Breast02 study in the treatment setting after T-DM1 treatment, and the first analysis of the Serena-2 study.
Most of these studies have the potential to significantly change the therapeutic landscape for patients with advanced breast carcinoma and show that the continued rapid development of new therapies is always producing new results.

**ZUSAMMENFASSUNG**

Eine Reihe von neuen Therapien hat in den letzten Jahren die Fortschritte in der Behandlung von Patientinnen mit fortgeschrittenem Mammakarzinom bestimmt. Diese Substanzen sind hauptsächlich die CDK4/6-Inhibitoren und weitere Substanzen, welche die endokrine Resistenz überwinden können, die oralen selektiven Östrogenrezeptor-Degradierer, die Antikörper-Medikament Konjugate (ADCs) und die PARP-Inhibitoren. In dieser Übersichtsarbeit werden die neuesten Studienergebnisse zusammengefasst und bewertet, die in den letzten Monaten veröffentlicht worden sind. Dies beinhaltet die Gesamtüberlebensdaten der Destiny-Breast03-Studie, die erste Analyse der CAPItello-291-Studie, den Vergleich einer CDK4/6-Inhibitor-Therapie mit Chemotherapie in der ersten Therapielinie (RIGHT Choice-Studie), die erste Analyse der Destiny-Breast02-Studie im Therapie-Setting nach T-DM1-Therapie und die erste Analyse der Serena-2-Studie.
Die meisten dieser Studien haben das Potenzial, die Therapielandschaft für Patientinnen mit fortgeschrittenem Mammakarzinom deutlich zu verändern, und zeigen, dass die Entwicklung neuer Therapien mit einer nach wie vor hohen Geschwindigkeit immer neue Ergebnisse produziert.

## Introduction

After the establishment of CDK4/6 inhibitors, PARP inhibitors, and the PI3 K inhibitor alpelisib, a whole series of new substances and studies have become the focus of interest in the treatment of patients with advanced HRpos/HER2neg breast carcinoma, including selective estrogen receptor degraders (SERD), new Akt kinase inhibitors, and the antibody-drug conjugates (ADC) trastuzumab deruxtecan and sacituzumab govitecan. Some of these drugs (sacituzumab govitecan and trastuzumab deruxtecan) are also relevant in patients with triple-negative breast carcinoma. In HER2-positive breast carcinoma, trastuzumab deruxtecan and tucatinib have set new standards. This review summarizes the latest findings that have been published in the past months, either as a full-length publication or at one of the major congresses, for example at the 2022 San Antonio Breast Cancer Symposium.

## Patients with Advanced HRpos/HER2neg Disease

### RIGHT Choice study – chemotherapy vs. ribociclib in first-line therapy

For patients with advanced HRpos/HER2neg breast carcinoma, the national and international guidelines uniformly recommend that all endocrine therapy options should be exhausted before chemotherapy is chosen as the treatment [1]. Only if there is a visceral crisis should chemotherapy be chosen as the treatment option [2]. Nevertheless, before the introduction of CDK4/6 inhibitors, 40–50% of advanced HRpos/HER2neg patients were treated with chemotherapy in the first line of therapy [3, 4, 5]. After the introduction of CDK4/6 inhibitors, this decreased to 10%–20% [6]. Based on these data from real-world surveys, analyses were also provided for the prognosis and comparison of the therapy groups (endocrine therapy vs. chemotherapy). All of these evaluations showed that patients treated with chemotherapy have a worse prognosis

[5, 6, 7]. A representation of these comparisons is shown in ▶ **Fig. 1**. The multivariate analyses showed that the choice of treatment had an independent influence on the prognosis [5, 6]. Nevertheless, these studies concluded that the poorer prognosis of patients with chemotherapy is attributed to selecting patients with a poorer prognosis when determining the treatment. This interpretation was put to the test by the publication of the RIGHT Choice study [8].

The RIGHT Choice study included patients with advanced HRpos/HER2neg breast carcinoma in the first line of therapy. A requirement was that patients had either symptomatic visceral metastases, a visceral crisis, rapid disease progression, or a clearly symptomatic, non-visceral disease [8]. According to the medical assessment, it should be a patient cohort for which polychemotherapy is indicated. Patients were randomized to treatment with ribociclib + letrozole (± goserelin) or a combination chemotherapy with one of the following chemotherapies: docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine. The primary study goal was progression-free survival (PFS). A large proportion of the 222 patients included in the study had symptomatic visceral metastases (67.6%), and most patients had de novo metastatic disease (64.9%) [8]. The median follow-up period was 24.1 months. When comparing the two randomization arms, the median PFS was significantly better in the ribociclib arm (24.0 months) than in the chemotherapy arm (12.3 months). The hazard ratio was 0.54 (95% CI: 0.36–0.79, $p < 0.007$) [8]. The time to response to therapy was very similar in both randomization arms (4.9 months in the ribociclib arm and 3.2 months in the chemotherapy arm). As expected, treatment-related severe adverse events were less frequent in the ribociclib arm (1.8%) than in the chemotherapy arm (8%) despite prolonged treatment. Quality of life analyses have not yet been reported.

The RIGHT Choice study challenges the paradigm of requiring chemotherapy for a rapid response in an aggressive disease. It underscores once again that all endocrine therapy options should be exhausted before using chemotherapy and that combination therapy with ribociclib and letrozole results in better PFS than chemotherapy.

## The efficacy of certain ADC therapies seems to be independent of target expression – analyses using sacituzumab govitecan in the TROPiCS-02 study as an example

The TROPiCS-02 study had already reported that progression-free survival and overall survival could be improved with treatment with sacituzumab govitecan compared to chemotherapy. The TROPiCS-02 study included HRpos/HER2neg patients who had already received 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 HRpos/HER2neg patients who had clearly undergone preliminary therapy were included in this study [9]. 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.

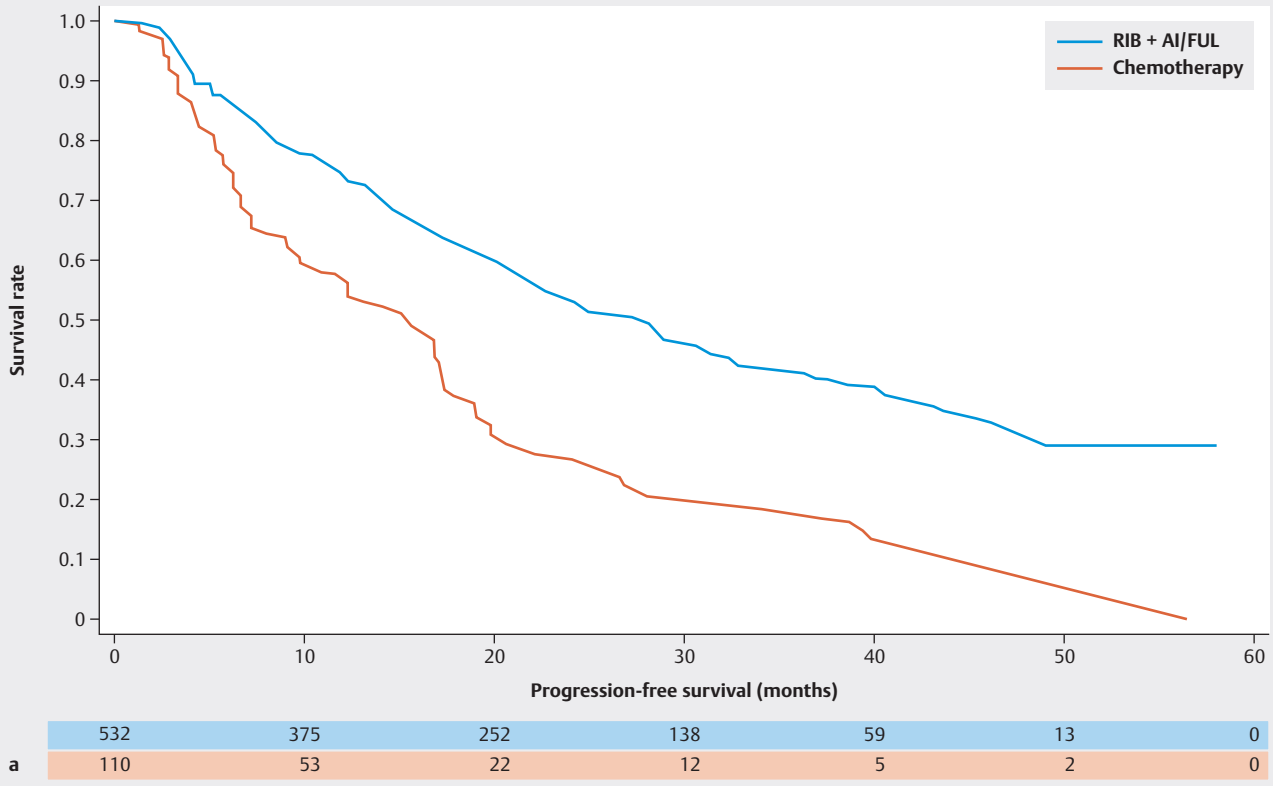
In some ADCs, it is suspected that efficacy can be achieved even at low expression of the target through a so-called bystander effect. This has already been shown for trastuzumab deruxtecan in HRpos/HER2neg, HER2-low-expressing tumors [10], and for sacituzumab govitecan in triple-negative tumors [11]. Now, the corresponding results for Trop2 expression have also been reported for the TROPiCS-02 study [12]. ▶ **Fig. 2** shows the hazard ratios for the various subgroups for progression-free survival and overall survival. The patients were divided into groups with an h-score (possible values 0–300) [0–10], [11–99], and [100–300]. For the two groups [11–99] and [100–300], the comparisons between the randomization arms were very similar. In the smaller group of patients with an h-score [0–10], the hazard ratio for progression-free survival was 0.89, which is higher than in the other two groups. However, in terms of overall survival, the hazard ratio was lower at 0.61 [12]. However, this group was small (n = 79) and also included 25 patients entirely without Trop2 expression [12]. These data show that efficacy does not appear to depend on Trop2 expression and that some effects of ADC need to be better understood.

## Camizestrant also improves progression-free survival

The substance group of oral selective estrogen receptor degraders (SERDs) is of particular interest because these therapies are better bioavailable than the SERD fulvestrant and may have better efficacy than aromatase inhibitors, especially in patients with a somatic *ESR1* mutation. For the oral SERD elacestrant, it has already been reported in the EMERALD study that in previously treated patients with advanced HRpos/HER2neg disease and endocrine resistance, progression-free survival can be improved with elacestrant compared to standard endocrine therapy [13, 14]. For the two SERDs giredestrant (acelERA study) and amcenestrant (AMEERA-3 study), no superiority compared to standard endocrine therapy could be demonstrated in a similar therapy situation [15, 16].

Due to the mechanism of action [17, 18] of SERDs, these substances are thought to have superiority over other endocrine therapy options in patients with an *ESR1* mutation. This was the case for the SERD elacestrant, so that elacestrant has only been approved in the USA in cases of a proven *ESR1* mutation [19].

Another study has now been published with positive results with camizestrant and the Serena-2 study [20]. The study included patients who had relapse or progression under endocrine therapy and thus showed signs of endocrine resistance. Patients were randomized to receive treatment with either fulvestrant or camizestrant 75 mg or camizestrant 150 mg. A total of 220 patients were included. Approximately one third of the patients were enrolled with progression in adjuvant therapy and two thirds with progression in the first line of endocrine therapy [20]. Approximately one third of patients (36.7%) also had an *ESR1* mutation. Both the group of patients, who were treated with 75 mg camizestrant (HR = 0.58; 95% CI: 0.41–0.81), as well as the patients who were treated with 150 mg camizestrant (HR = 0.67; 95% CI: 0.48–0.92) had longer progression-free survival compared to fulvestrant therapy [20]. This was also the case for the group of patients who had

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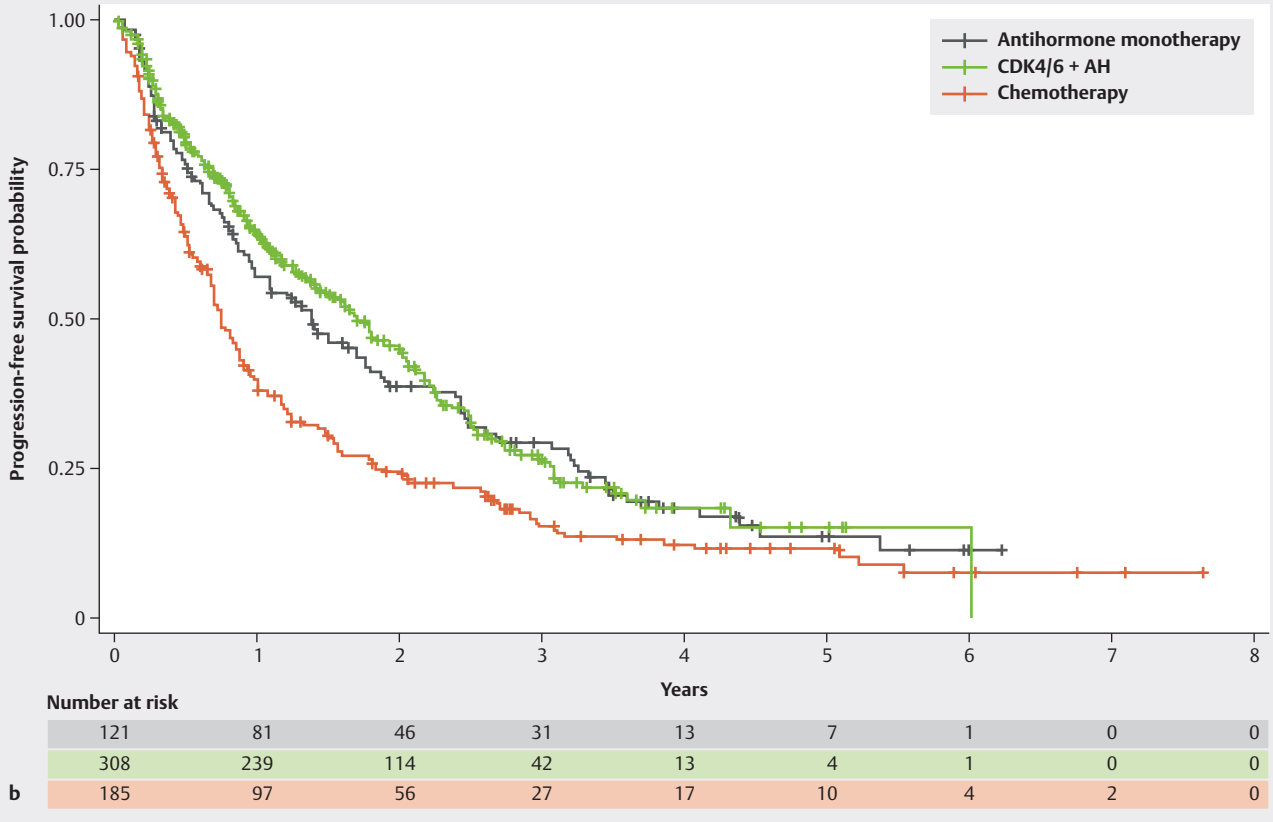
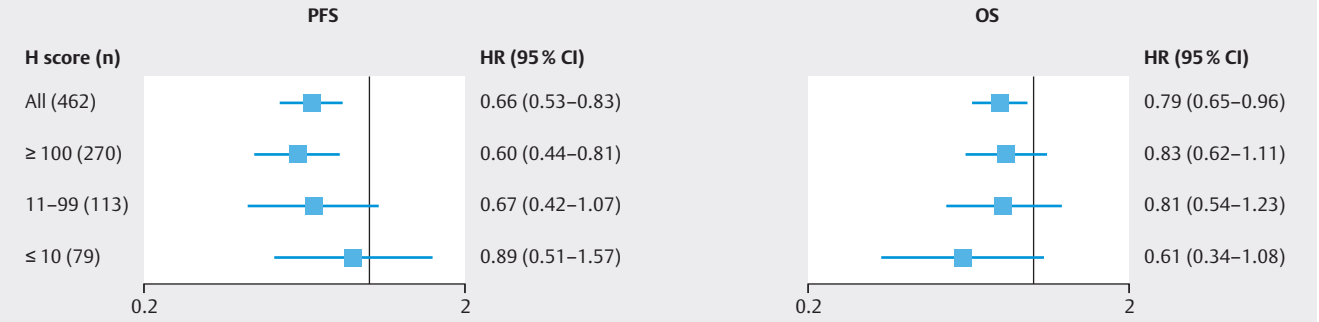
| | 532 | 375 | 252 | 138 | 59 | 13 | 0 |
| a | 110 | 53 | 22 | 12 | 5 | 2 | 0 |




Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 121 | 81 | 46 | 31 | 13 | 7 | 1 | 0 | 0 |
| | 308 | 239 | 114 | 42 | 13 | 4 | 1 | 0 | 0 |
| b | 185 | 97 | 56 | 27 | 17 | 10 | 4 | 2 | 0 |

▶ **Fig. 1** Representation of progression-free survival (PFS) in the two studies, **a** RIBANNA [7] and **b** PRAEGNANT [6].




▶ **Fig. 2** Hazard ratios for the subgroups of the TROPiCS-02 study stratified according to Trop2 expression (HR = hazard ratio; OS = overall survival; PFS = progression-free survival).

been pretreated with a CDK4/6 inhibitor. No treatment benefit could be demonstrated in patients without an *ESR1* mutation, whereas the benefit was considerable in patients with an *ESR1* mutation (▶ **Table 1**). In the group of patients with an *ESR1* mutation and treatment with camizestrant 150 mg, the median PFS was extended from 2.2 months with fulvestrant to 9.2 months [20]. With regard to side effects, grade 1 and grade 2 sinus bradycardia occurred more frequently with camizestrant, with 75% mg of camizestrant in 5.4% of patients and 150% for camizestrant mg in 25% of patients.

In particular, the results in the group of patients with an *ESR1* mutation motivate support for relevant study concepts investigating whether patients with an *ESR1* mutation are more likely to benefit from a SERD in combination with a CDK4/6 inhibitor or the continuation of treatment with a CDK4/6 inhibitor and aromatase inhibitor, such as the SERENA-6 study [21].

## PROTAC SERDs with initial efficacy data from a phase II study

The active substance platform PROTAC (Proteolysis Targeting Chimera) has been introduced as a new concept in the degradation of proteins. With ARV-471, a SERD is available as one of the first PROTAC substances. On the one hand, the hetero-bifunctional molecule has a ligand for the protein of interest (in this case the estrogen receptor), and on the other hand another ligand that serves as a substrate for the E3 ubiquitin ligase complex. This binds the protein to be degraded with the ubiquitin-proteasome system, which triggers degradation [17, 22]. Initial efficacy data on a small cohort have already been presented in the past [22]. Further data on a larger cohort in the form of a phase II study have now been presented [23]. The VERITAC study included 71 patients with severely pretreated, advanced HRpos/HER2neg breast carcinoma. On median, the patients had already received three lines of therapy in the metastatic situation. All had received preliminary therapy with a CDK4/6 inhibitor, 79% with fulvestrant and 45% with chemotherapy in the metastatic situation. Overall, 57.7% of patients had *ESR1* mutations after the extensive preliminary therapies. The median PFS was 3.7 months (95% CI; 1.9–8.3) for the overall population and 5.7 months (95% CI: 3.6–9.4) for patients with an *ESR1* mutation. The clinical benefit rate (stable disease and remissions) was 38.0% (95% CI: 26.8–50.3) for the overall cohort and 51.2% (95% CI: 35.1–67.1) for patients with an *ESR1* mutation. With extensive preliminary treatment, these results are very promising. The substance is being further developed in both the metastatic situation and the neoadjuvant situation [24, 25, 26]. The neoadjuvant TACTIVE-N/ TRIO-048 study is already recruiting, including in Germany among other countries.

## First randomized trial of capivasertib (Akt kinase inhibitor) published

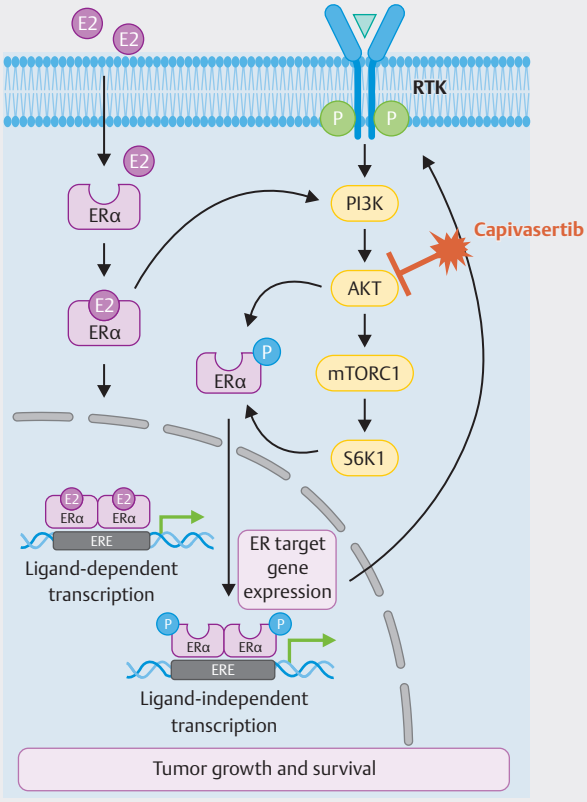
The CAPItello-291 study presented the first large-scale randomized phase III trial of the Akt kinase inhibitor capivasertib [27]. It is thought that genomic alterations in the PI3K/Akt kinase signaling pathway (▶ **Fig. 3**) lead to activation and subsequent tumor growth, proliferation, and metastasis. These genomic alterations are thought to be in the *AKT1*, *PIK3CA*, and *PTEN* genes. However, it is also known that the activation of the signaling pathway can occur without a genomic alteration in one of these genes [28].

Capivasertib is an inhibitor of all isoforms of Akt kinase (AKT1/AKT2/AKT3). In the phase II FAKTION study of 140 patients, it was already shown that adding capivasertib to fulvestrant improved progression-free survival and overall survival [29]. However, no patients with a CDK4/6 pretreatment were included in this study, and testing for genomic alterations was performed at different points in time using different methods.

The CAPItello-291 study included a total of 708 patients with advanced HRpos/HER2neg breast carcinoma who had relapse during or up to 12 months after adjuvant aromatase inhibitor therapy or who had progression during aromatase inhibitor therapy in the metastatic situation. Up to two lines of endocrine therapy were allowed in the advanced therapy situation, and a maximum of one chemotherapy. Patients were randomized to either therapy with capivasertib and fulvestrant or therapy with fulvestrant monotherapy. Progression-free survival was the primary study objective, and overall survival was one of the secondary study objectives. Of the patients included in the study, most patients (> 80 %) had already received at least one endocrine therapy for advanced disease, and approximately 70 % had taken a CDK4/6 inhibitor prior to inclusion in the study [27]. Genomic alterations were investigated using FoundationOne or Burning Rock assays. A total of 40.8% (n = 289)

▶**Table 1** Comparison of progression-free survival times between the randomization arms of the Serena-2 study in the total population and stratified according to ESR1 mutation stats [20].

| Population | n | HR (95% CI)<br>Camizenstrant 75 mg vs. fulvestrant | HR (95% CI)<br>Camizenstrant 150 mg vs. fulvestrant |
|---|---|---|---|
| Total population | 220 | 0.58 (0.41–0.81) | 0.67 (0.48–0.92) |
| Patients with ESR1 mutation at baseline | 83 | 0.33 (0.18–0.58) | 0.55 (0.33–0.89) |
| Patients without ESR1 mutation at baseline | 134 | 0.78 (0.50–1.22) | 0.76 (0.48–1.20) |




▶ **Fig. 3** Illustration of the PI3 K-AKT kinase signaling pathway and its crosstalk with the estrogen signaling pathway (source: Alves CL, Ditzel HJ. Drugging the PI3 K/AKT/mTOR Pathway in ER+ Breast Cancer. Int J Mol Sci 2023; 24. doi:10.3390/ijms24054522, red marking and labeling supplemented with capivasertib, Creative Commons Attribution [CC BY] license, https://creativecommons.org/licenses/by/4.0/).

of the patients had an alteration in *PIK3CA*, *AKT1*, or *PTEN*. Most of the patients had a mutation exclusively in the *PIK3CA* gene (219 out of 289 patients with a genomic alteration) [27].

In the overall population, the addition of capivasertib improved the median PFS from 3.6 months (95% CI: 2.8–3.7) to 7.2 months (95% CI: 5.5–7.4). The hazard ratio was 0.60 (95% CI: 0.51–0.71, p < 0.001). The therapeutic effect was consistent across all subgroups, especially in the group of patients pretreated with CDK4/6 inhibitors (HR = 0.62; 95% CI: 0.51–0.75). With regard to the abovementioned genomic alterations, although a slightly lower hazard ratio was found in the group of patients with an AKT pathway alteration (HR = 0.50; 95% CI 0.38–0.65), an effect was also detectable in the group of patients without alteration (HR = 0.70; 95% CI: 0.56–0.88). An exploratory analysis of overall survival showed an initial indication of an overall survival benefit with 87 events in the capivasertib arm and 108 events in the fulvestrant monotherapy arm, with a hazard ratio of 0.74 (95% CI: 0.56–0.98). This trend was even slightly lower in the group of patients with an alteration in the AKT signaling pathway (HR = 0.69; 95% CI: 0.45–1.05). With regard to side effects, additional diarrhea, nausea/vomiting, rash, and fatigue have mainly been reported. The rate of treatment discontinuation due to side effects was 13% in the capivasertib arm.

With capivasertib, a new substance has now been established in a phase III trial after everolimus, the CDK4/6 inhibitors, and alpelisib, which can overcome endocrine resistance through a combination with endocrine therapy for a relevant proportion of patients. The trend in terms of overall survival is promising. However, overall survival can only be adequately assessed when more events have occurred and the first planned analysis with regard to this endpoint is performed.

## Patients with HER2-Positive Advanced Disease

### Destiny Breast 03 study – overall survival data positive

The Destiny Breast 03 study has already established in the first analysis the superiority of T-DXd over T-DM1 in terms of progression-free survival [30]. Although the overall survival data indicated that the T-DXd arm was superior to T-DM1, no statistically significant superiority could be demonstrated with regard to this analysis [30].

A further evaluation with a longer follow-up period has now been presented [31, 32]. The median follow-up times were 28.4 months in the T-DXd arm and 26.5 months in the T-DM1 arm. The median OS was not achieved in any of the two randomization arms. The 24-month survival rates were 77.4% (71.7–82.1%) in the T-DXd arm and 69.9% (63.7–75.2%) in the T-DM1 arm. The hazard ratio was 0.64 (95% CI: 0.47–0.87, P < 0.0037). This difference was statistically significant and largely consistent in the subgroup analyses performed.

A new analysis was also performed for progression-free survival. With the longer follow-up period, the results were very similar to those of the previous analysis. The hazard ratio was 0.33 (95% CI: 0.26–0.43, p < 0.000001). The median PFS was 28.8 months

(95% CI: 22.4–37.9 months) in the T-DXd arm and 6.8 months (95% CI: 5.6–8.2 months) in the T-DM1 arm [31, 32].

In the previous analysis, no deaths have occurred to date as a consequence of interstitial lung disease. This could be confirmed in the analysis with the longer follow-up period. Furthermore, no deaths were observed due to this side effect.

With the excellent data in terms of overall survival, a new question arises in this and similar studies. In the T-DXd arm, clinical complete remission could be seen in 21.1% of cases (n = 55). Given the high frequency, the question arises as to whether this clinical response can be used to predict long-term survival. Appropriate analyses should be planned for the future.

### Destiny Breast 02 study – trastuzumab deruxtecan after T-DM1 treatment

The Destiny-Breast 02 study was conducted in parallel with the Destiny-Breast 03 study [33]. However, this study included patients who had already completed treatment with T-DM1. Thus, in terms of the study population, all patients had preliminary therapy with T-DM1 and approximately 80% had preliminary therapy with pertuzumab and trastuzumab. Randomization was performed with a 2 : 1 ratio. 406 patients received T-DXd and 202 patients received treatment of the physician's choice (TPC arm), which was either capecitabine + trastuzumab or capecitabine + lapatinib. Most patients were treated as part of the study in the third (45%) or fourth line of therapy (30%). The important subgroup of patients with brain metastases consisted of 18.2% in the T-DXd arm and 17.8% in the TPC arm [33].

The median PFS was 17.8 months (95% CI: 14.3–20.8) in the T-DXd arm and 6.9 months (95% CI: 5.5–8.4) in the TPC arm. This corresponded to a hazard ratio of 0.36 (95% CI: 0.28–0.45). There was no difference in efficacy in patients with (HR = 0.35; 95% CI: 0.20–0.61) and without brain metastases (HR = 0.38; 95% CI: 0.29–0.48) [33].

There was also a clear difference in terms of overall survival. The median overall survival in the T-DXd arm was 39.2 months (95% CI: 32.7–NE) and 26.5 months (95% CI: 21.0–NE). This corresponded to a hazard ratio of 0.66 (95% CI: 0.50–0.86) in favor of T-DXd [33].

In the context of this study, no new safety signals were seen, in particular no deaths as a consequence of interstitial pneumonitis. Nevertheless, it is important to consistently diagnose respiratory symptoms under T-DXd, to consider corticosteroid treatment, and to make appropriate dose changes and interruptions if necessary.

## Outlook

With elacestrant and camizestrant, two SERDs, especially with an *ESR1* mutation, have shown that they have high efficacy compared to standard endocrine therapy. They would have the potential to establish themselves as new combination partners for the CDK4/6 inhibitors or after treatment with CDK4/6 inhibitors after corresponding results. With capivasertib, endocrine resistance could be overcome for a relevant proportion of HRpos/HER2neg patients after everolimus, the CDK4/6 inhibitors, and alpelisib for further combination therapy. The next important step must be to gain a better understanding of the resistance mechanisms and the chronological sequence of the resistance mechanisms. For this purpose, data must be collected from a large number of patients under the appropriate therapies. This task will mainly involve studies in the real-world setting. Two of these studies, which are active in Germany, are the CAPTOR-BC and the MINERVA study [34, 35, 36]. The prospective collection of the necessary clinical and molecular data will provide an opportunity to better understand the mechanisms of progression and be able to plan the ideal treatment sequencing for patients.

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## Conflict of Interest

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## References/Literatur


[1] Ditsch N, Kolberg-Liedtke C, Friedrich M et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2021. Breast Care (Basel) 2021; 16: 214–227. doi:10.1159/000516419

[2] Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31: 1623–1649. doi:10.1016/j.annonc.2020.09.010

[3] Schneeweiss A, Ettl J, Luftner D et al. Initial experience with CDK4/6 inhibitor-based therapies compared to antihormone monotherapies in routine clinical use in patients with hormone receptor positive, HER2 negative breast cancer – Data from the PRAEGNANT research network for the first 2 years of drug availability in Germany. Breast 2020; 54: 88–95. doi:10.1016/j.breast.2020.08.011

[4] Hartkopf AD, Huober J, Volz B et al. Treatment landscape of advanced breast cancer patients with hormone receptor positive HER2 negative tumors – Data from the German PRAEGNANT breast cancer registry. Breast 2018; 37: 42–51. doi:10.1016/j.breast.2017.10.002

[5] Lobbezoo DJ, van Kampen RJ, Voogd AC et al. In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium. Ann Oncol 2016; 27: 256–262. doi:10.1093/annonc/mdv544

[6] Engler T, Fasching PA, Luftner D et al. Implementation of CDK4/6 Inhibitors and its Influence on the Treatment Landscape of Advanced Breast Cancer Patients – Data from the Real-World Registry PRAEGNANT. Geburtshilfe Frauenheilkd 2022; 82: 1055–1067. doi:10.1055/a-1880-0087

[7] Jackisch C, Brucker C, Decker T et al. Abstract P4–01–01: RIBANNA 5th interim analysis: Matched-pair analysis of progression-free survival (PFS) across treatment cohorts and comparison of frontline ribociclib + endocrine therapy PFS data from RIBANNA vs MONALEESA trials, in HR+, HER2– ABC. San Antonio Breast Cancer Symposium 2022. Cancer Res 2023; 83 (Suppl 5): P4–01–01. doi:10.1158/1538-7445.SABCS22-P4-01-01

[8] Lu YS, Bin Mohd Mahidin EI, Azim H et al. Abstract GS1–10: Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy. San Antonio Breast Cancer Symposium 2022. Cancer Res 2023; 83 (Suppl 5): GS1–10. doi:10.1158/1538-7445.SABCS22-GS1-10

[9] Rugo HS, Bardia A, Marmé F et al. Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2−) advanced breast cancer. J Clin Oncol 2022; 40: LBA1001. doi:10.1200/JCO.2022.40.17_suppl.LBA1001

[10] Modi S, Saura C, Yamashita T et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020; 382: 610–621. doi:10.1056/NEJMoa1914510

[11] Hurvitz SA, Tolaney SM, Punie K et al. Abstract GS3–06: Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. San Antonio Breast Cancer Symposium 2020. Cancer Res 2021; 81 (Suppl 4): GS3–06. doi:10.1158/1538-7445.SABCS20-GS3-06

[12] Rugo HS, Bardia A, Marmé F et al. Abstract GS1–11: Sacituzumab Govitecan (SG) vs Treatment of Physician's Choice (TPC): Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients (Pts) With HR+/HER2– Metastatic Breast Cancer (mBC). San Antonio Breast Cancer Symposium 2022. Cancer Res 2023; 83 (Suppl 5): GS1–11. doi:10.1158/1538-7445.SABCS22-GS1-11

[13] Bidard FC, Kaklamani VG, Neven P et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol 2022; 40: 3246–3256. doi:10.1200/JCO.22.00338

[14] Bardia A, Neven P, Streich G et al. Abstract GS2–02: Elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2− advanced/metastatic breast cancer (mBC) following progression on prior endocrine and CDK4/6 inhibitor therapy: Results of EMERALD phase 3 trial. San Antonio Breast Cancer Symposium 2021. Cancer Res 2022; 82 (Suppl 4): GS2–02. doi:10.1158/1538-7445.SABCS21-GS2-02

[15] Tolaney SM, Chan A, Petrakova K et al. AMEERA-3, a phase II study of amcenestrant (AMC) versus endocrine treatment of physician's choice (TPC) in patients (pts) with endocrine-resistant ER+/HER2− advanced breast cancer (aBC). Ann Oncol 2022; 33 (Suppl 7): S80–S121. doi:10.1016/annonc/annonc1089

[16] Jimenez MM, Lim E, Gregor MCM et al. Giredestrant (GDC-9545) vs physician choice of endocrine monotherapy (PCET) in patients (pts) with ER+, HER2– locally advanced/metastatic breast cancer (LA/mBC): Primary analysis of the phase II, randomised, open-label acelERA BC study. Ann Oncol 2022; 33 (Suppl 7): S808–S869. doi:10.1016/annonc/annonc1089

[17] Luftner D, Lux MP, Fehm TN et al. Update Breast Cancer 2022 Part 6 – Advanced-Stage Breast Cancer. Geburtshilfe Frauenheilkd 2023; 83: 299–309. doi:10.1055/a-2018-9184

[18] Aktas B, Fehm TN, Welslau M et al. Update Breast Cancer 2022 Part 4 – Advanced-Stage Breast Cancer. Geburtshilfe Frauenheilkd 2022; 82: 922–931. doi:10.1055/a-1912-7362

[19] U.S. Department of Health and Human Services Food and Drug Administration (FDA). Highlights of Prescribing Information Orserdu. 2023. Accessed April 11, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217639s000lbl.pdf

[20] Oliveira M, Pominchuck D, Nowecki Z et al. Abstract GS3–02: GS3–02 Camizestrant, a next generation oral SERD vs fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose Phase 2 SERENA-2 trial. Cancer Res 2023; 83: GS3–02. doi:10.1158/1538-7445.Sabcs22-gs3-02

[21] clinicaltrials.gov. Phase III Study to Assess AZD9833+ CDK4/6 Inhibitor in HR+/HER2-MBC With Detectable ESR1m Before Progression (SERENA-6) (SERENA-6). 2021. Accessed October 24, 2021 at: https://clinicaltrials.gov/ct2/show/NCT04964934

[22] Snyder LB, Flanagan JJ, Qian Y et al. Abstract 44: The discovery of ARV-471, an orally bioavailable estrogen receptor degrading PROTAC for the treatment of patients with breast cancer. Cancer Res 2021; 81: 44. doi:10.1158/1538-7445.Am2021-44

[23] Schott AF, Hurvitz S, Ma C et al. Abstract GS3–03: GS3–03 ARV-471, a PROTAC® estrogen receptor (ER) degrader in advanced ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer: phase 2 expansion (VERITAC) of a phase 1/2 study. Cancer Res 2023; 83: GS3–03. doi:10.1158/1538-7445.Sabcs22-gs3-03

[24] Fasching PA, Clifton K, Katashvili Z et al. 154TiP TACTIVE-N: Open-label, randomized, noncomparative neoadjuvant phase 2 study of ARV-471, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, or anastrozole in postmenopausal women with ER+/human epidermal growth factor receptor 2 (HER2)- localized breast cancer. ESMO Open 2023; 8 (Suppl 4): 101493. doi:10.1016/j.esmoop.2023.101493

[25] Clinicaltrials.gov. A Trial Using ARV-471 or Anastrozole in Post-Menopausal Women With Breast Cancer Prior to Surgery. 2023. Accessed April 11, 2023 at: https://clinicaltrials.gov/ct2/show/NCT05549505

[26] Clinicaltrials.gov. ARV-471 in Combination With Everolimus for the Treatment of Advanced or Metastatic ER+, HER2- Breast Cancer. 2023. Accessed April 11, 2023 at: https://clinicaltrials.gov/ct2/show/NCT05501769

[27] Turner N, Oliveira M, Howell SJ et al. Abstract GS3–04: GS3–04 Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial. Cancer Res 2023; 83: GS3–04. doi:10.1158/1538-7445.Sabcs22-gs3-04

[28] Alves CL, Ditzel HJ. Drugging the PI3K/AKT/mTOR Pathway in ER+ Breast Cancer. Int J Mol Sci 2023; 24: 4522. doi:10.3390/ijms24054522

[29] Howell SJ, Casbard A, Carucci M et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol 2022; 23: 851–864. doi:10.1016/S1470-2045(22)00284-4

[30] Cortes J, Kim SB, Chung WP et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med 2022; 386: 1143–1154. doi:10.1056/NEJMoa2115022

[31] Hurvitz S, Hegg R, Chung W-P et al. Abstract GS2–02: GS2–02 Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated survival results of the randomized, phase 3 study DESTINY-Breast03. Cancer Res 2023; 83: GS2–02. doi:10.1158/1538-7445.Sabcs22-gs2-02

[32] Hurvitz SA, Hegg R, Chung WP et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 2023; 401: 105–117. doi:10.1016/S0140-6736(22)02420-5

[33] Krop I, Park YH, Kim S-B et al. Abstract GS2–01: GS2–01 Trastuzumab deruxtecan vs physician's choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: primary results of the randomized, phase 3 study DESTINY-Breast02. Cancer Res 2023; 83: GS2–01. doi:10.1158/1538-7445.Sabcs22-gs2-01

[34] clinicaltrials.gov. Comprehensive Analysis of Spatial, Temporal and Molecular Patters of Ribociclib Efficacy and Resistance in Advanced Breast Cancer Patients (CAPTOR-BC). 2022 . Accessed July 16, 2022 at: https://clinicaltrials.gov/ct2/show/NCT05452213

[35] Fasching PA. CAPTOR-BC: Gemeinsam Forschen für eine individualisierte Ribociclib-Therapie. Senologiekongress 2022. 2022. Accessed June 26, 2022 at: https://www.senologiekongress.de/xconfig/upload/files/Programme/Seno2022_Programm.pdf

[36] clinicaltrials.gov. Combination of Abemaciclib and Endocrine Therapy in Hormone Receptor Positive HER2 Negative Locally Advanced or Metastatic Breast Cancer With Focus on Digital Side Effect Management (MINERVA). 2022. Accessed June 26, 2022 at: https://clinicaltrials.gov/ct2/show/NCT05362760