

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

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



### Authors

Michael P. Lux<sup>1</sup>, Andreas D. Hartkopf<sup>2</sup>, Tanja N. Fehm<sup>3</sup>, Manfred Welslau<sup>4</sup>, Volkmar Müller<sup>5</sup>, Florian Schütz<sup>6</sup>, Peter A. Fasching<sup>7</sup>, Wolfgang Janni<sup>2</sup>, Isabell Witzel<sup>8</sup>, Christoph Thomssen<sup>9</sup>, Milena Beierlein<sup>7</sup>, Erik Belleville<sup>10</sup>, Michael Untch<sup>11</sup>, Marc Thill<sup>12</sup>, Hans Tesch<sup>13</sup>, Nina Ditsch<sup>14</sup>, Bahriye Aktas<sup>15</sup>, Maggie Banys-Paluchowski<sup>16</sup>, Cornelia Kolberg-Liedtke<sup>17</sup>, Achim Wöckel<sup>18</sup>, Hans-Christian Kolberg<sup>19</sup>, Nadia Harbeck<sup>20</sup>, Rupert Bartsch<sup>21</sup>, Andreas Schneeweiss<sup>22</sup>, Johannes Ettl<sup>23</sup>, Rachel Würstlein<sup>20</sup>, David Krug<sup>24</sup>, Florin-Andrei Taran<sup>25</sup>, Diana Lüftner<sup>26</sup>, Elmar Sticker<sup>27</sup>

### Affiliations

- 1 Klinik für Gynäkologie und Geburtshilfe, Frauenklinik St. Louise, Paderborn, St. Josefs-Krankenhaus, Salzkotten, St. Vincenz Krankenhaus GmbH, Paderborn, Germany
- 2 Department of Gynecology and Obstetrics, Ulm University Hospital, Ulm, Germany
- 3 Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Düsseldorf, Germany
- 4 Onkologie Aschaffenburg, Aschaffenburg, Germany
- 5 Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany
- 6 Gynäkologie und Geburtshilfe, Diakonissen-Stiftungs-Krankenhaus Speyer, Speyer, Germany
- 7 Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
- 8 Klinik für Gynäkologie, Universitätsspital Zürich, Zürich, Switzerland
- 9 Department of Gynaecology, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
- 10 ClinSol GmbH & Co KG, Würzburg, Germany
- 11 Clinic for Gynecology and Obstetrics, Breast Cancer Center, Gynecologic Oncology Center, Helios Klinikum Berlin Buch, Berlin, Germany
- 12 Department of Gynecology and Gynecological Oncology, Agaplesion Markus Krankenhaus, Frankfurt am Main, Germany
- 13 Oncology Practice at Bethanien Hospital, Frankfurt am Main, Germany
- 14 Department of Gynecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany
- 15 Department of Gynecology, University of Leipzig Medical Center, Leipzig, Germany
- 16 Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany
- 17 Department of Gynecology and Obstetrics, University Hospital Essen, Essen, Germany
- 18 Department of Gynecology and Obstetrics, University Hospital Würzburg, Würzburg, Germany
- 19 Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Germany
- 20 Breast Center, Department of Gynecology and Obstetrics and CCC Munich LMU, LMU University Hospital, München, Germany
- 21 Department of Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria
- 22 National Center for Tumor Diseases, University Hospital and German Cancer Research Center, Heidelberg, Germany
- 23 Klinik für Frauenheilkunde und Gynäkologie, Klinikum Kempten, Klinikverbund Allgäu, Kempten, Germany
- 24 Klinik für Strahlentherapie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany
- 25 Department of Gynecology and Obstetrics, University Hospital Freiburg, Freiburg, Germany
- 26 Medical University of Brandenburg Theodor-Fontane, Immanuel Hospital Märkische Schweiz, Buckow, Germany
- 27 Department of Obstetrics and Gynecology, Center for Integrated Oncology (CIO Aachen, Bonn, Cologne, Düsseldorf), University Hospital of RWTH Aachen, Aachen, Germany

### Key words

breast cancer, metastatic, endocrine therapy, antibody drug conjugate, chemotherapy

### Schlüsselwörter

Brustkrebs, metastatisch, endokrine Therapie, Antikörper-Medikament-Konjugat, Chemotherapie

received 13.4.2023

accepted 14.4.2023

## Bibliography

Geburtsh Frauenheilk 2023; 83: 664–672

DOI 10.1055/a-2074-0125

ISSN 0016-5751


© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

Georg Thieme Verlag KG, Rüdigerstraße 14,  
70469 Stuttgart, Germany

## Correspondence

Prof. Peter A. Fasching, MD  
Erlangen University Hospital, Department of  
Gynecology and Obstetrics, Comprehensive Cancer  
Center Erlangen-EMN  
Friedrich-Alexander University Erlangen-Nuremberg  
Universitätsstr. 21–23  
91054 Erlangen, Germany  
[peter.fasching@uk-erlangen.de](mailto:peter.fasching@uk-erlangen.de)  
[peter.fasching@fau.de](mailto:peter.fasching@fau.de)

 Deutsche Version unter:  
<https://doi.org/10.1055/a-2074-0125>.

## 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 PI3K 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 ( $\pm$  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.

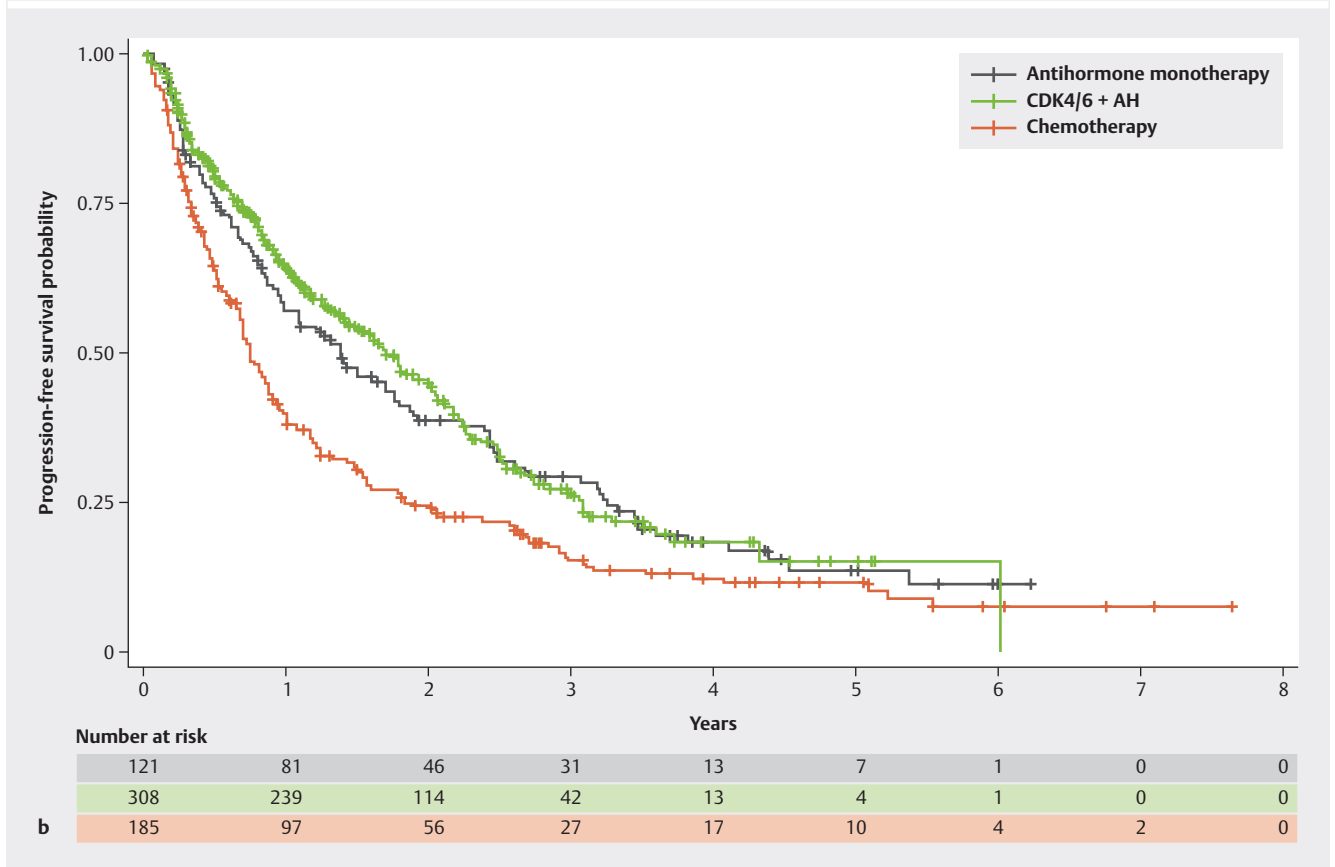
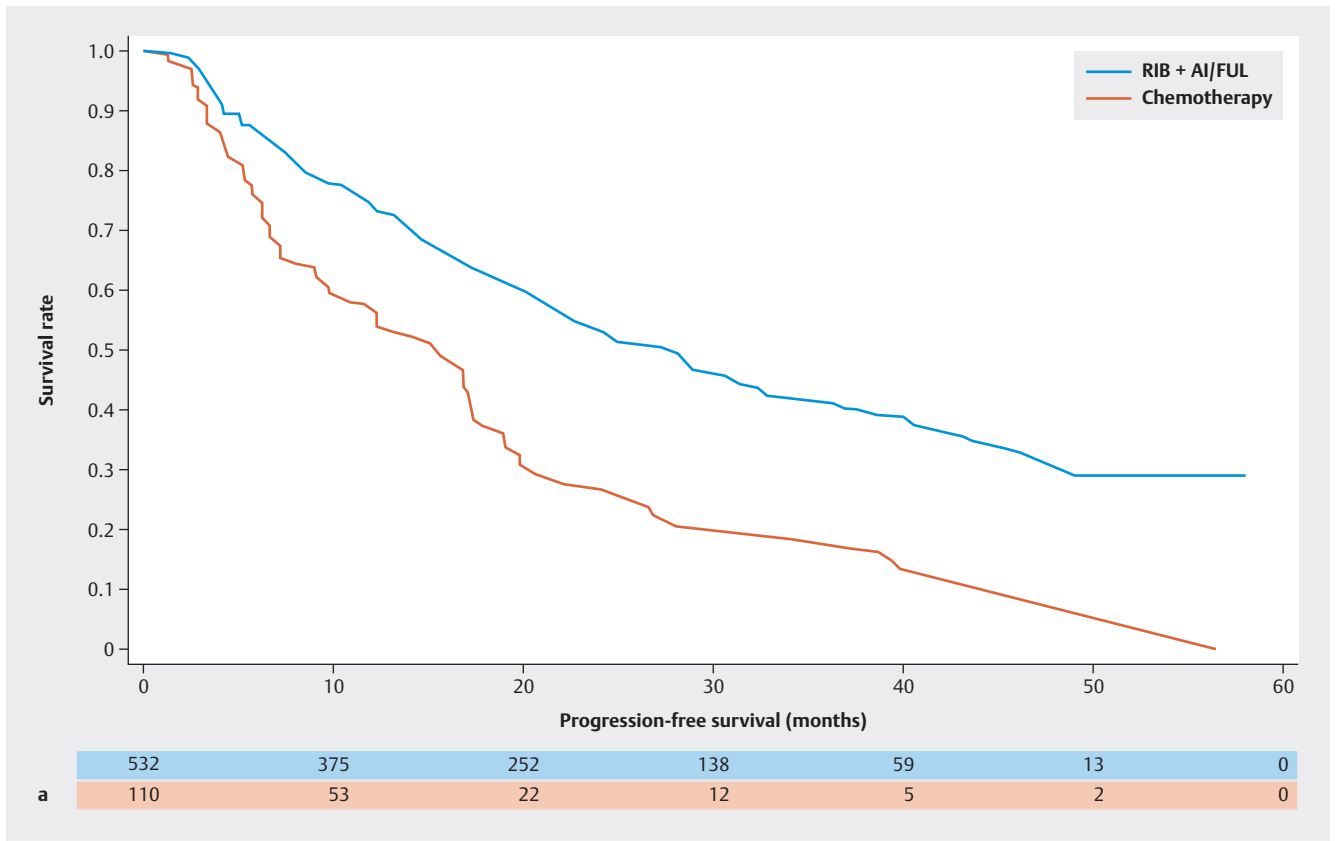
In some ADCs, it is suspected that efficacy can be achieved even at low expression of the target through a so-called bystander effect. This has already been shown for trastuzumab deruxtecan in HRpos/HER2neg, HER2-low-expressing tumors [10], and for sacituzumab govitecan in triple-negative tumors [11]. 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

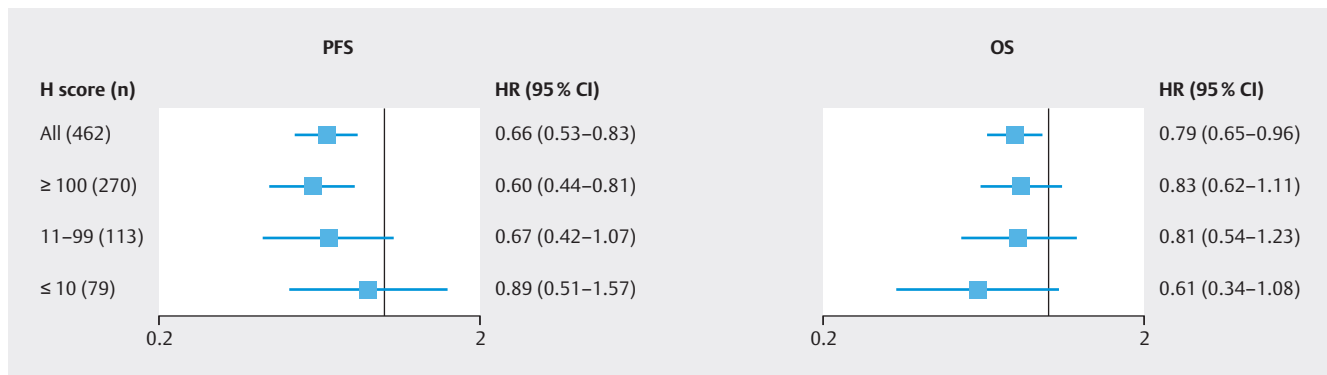
The substance group of oral selective estrogen receptor degraders (SERDs) is of particular interest because these therapies are better bioavailable than the SERD fulvestrant and may have better efficacy than aromatase inhibitors, especially in patients with a somatic *ESR1* mutation. For the oral SERD 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



► 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

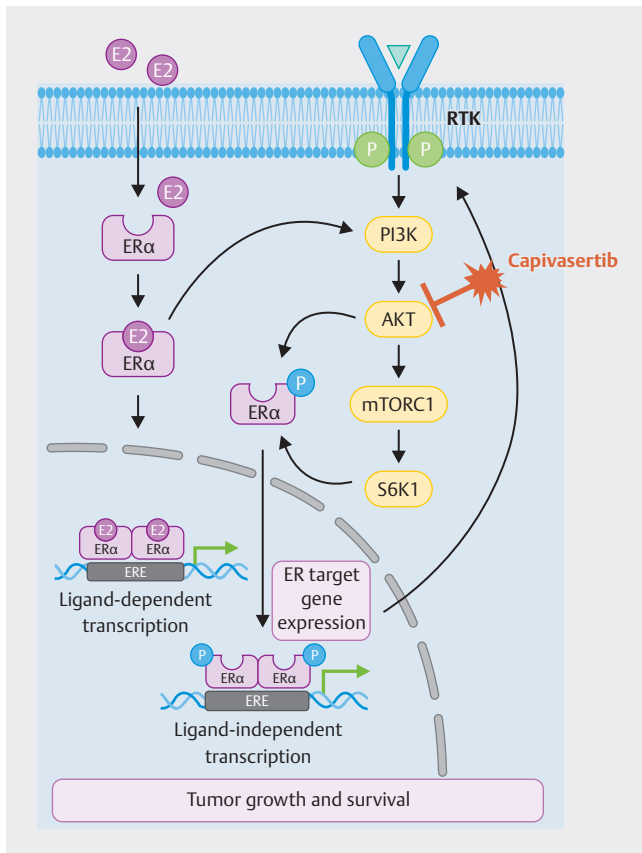
The CAPItello-291 study presented the first large-scale randomized phase III trial of the Akt kinase inhibitor capivasertib [27]. It is thought that genomic alterations in the PI3K/Akt kinase signaling pathway (► **Fig. 3**) lead to activation and subsequent tumor growth, proliferation, and metastasis. 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) Camizenstrant 75 mg vs. fulvestrant	HR (95% CI) 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 cappingasertib, 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 cappingasertib 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 cappingasertib 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 cappingasertib arm.

With cappingasertib, 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 cypivasertib, 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.

### Acknowledgement

This paper was partly developed as a result of funding from the companies onkowissen.de, Gilead, Lilly, Novartis, Pfizer, and MSD. None of the companies had any part in the preparation and recommendations of this manuscript. The authors are solely responsible for the content of the manuscript.

### Conflict of Interest

B. A. received honoraria and travel grants from AstraZeneca, Gilead, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo and Pfizer.  
 M. B.-P. received honoraria for lectures and advisory role from Roche, Novartis, Pfizer, pfm, Eli Lilly, Onkowissen, Seagen, Eisai, AstraZeneca, Amgen, Samsung, MSD, GSK, Daiichi Sankyo, Gilead, Sirius Pintuition, Pierre Fabre, and study support from Mammotome, Endomag and Merit Medical.  
 E. B. received honoraria from Gilead, Ipsen, Sanofi, Sandoz, SunPharma, AstraZeneca, Novartis, Hexal, BMS, Lilly, Pfizer, Roche, MSD, BBraun and onkowissen.de for clinical research management and/or medical education activities.  
 N. D. has received honoraria from MSD, Roche, AstraZeneca, Teva, Pfizer, Novartis, Seagen, Gilead, MCI Healthcare.  
 P. A. F. reports personal fees from Novartis, grants from Biontech, personal fees from Pfizer, personal fees from Daiichi Sankyo, personal fees from AstraZeneca, personal fees from Eisai, personal fees from Merck Sharp & Dohme, grants from Cepheid, personal fees from Lilly, personal fees from Pierre Fabre, personal fees from SeaGen, personal fees from Roche, personal fees from Hexal, personal fees from Agendia, personal fees from Gilead.  
 T. N. F. has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Amgen, Celgene, Daiichi Sankyo, Roche, Novartis and Pfizer.  
 A. D. H. received speaker and consultancy honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo, Hexal and Pfizer.  
 N. H. received honoraria for lectures and/or consulting from Amgen, AstraZeneca, Daiichi Sankyo, Exact Sciences, Gilead, Lilly, MSD, Mylan, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Seagen.  
 W. J. has received research Grants and/or honoraria from Sanofi-Aventis, Daiichi Sankyo, Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, GSK, Eisai, Cellgene and Johnson & Johnson.  
 H.-C. K. has received honoraria from Pfizer, Seagen, Novartis, Roche, Genomic Health/Exact Sciences, Amgen, AstraZeneca, Riemsler, Carl Zeiss Meditec, Teva, Theraclion, Janssen-Cilag, GSK, LIV Pharma, Lilly, SurgVision, Onkowissen, Gilead, Daiichi Sankyo and MSD, travel support from Carl Zeiss, Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo, Tesaro and owns stock of Theraclion SA and Phaon Scientific GmbH.

D. L. received honoraria from Amgen, AstraZeneca, Eli Lilly, High5 md, Gilead, GSK, Loral, MSD, Novartis, Onkowieden, Pfizer, Seagen, Teva. M. P. L. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer, Eisai, Gilead, Exact Sciences, Pierre Fabre, Grünenthal, Daiichi Sankyo, PharmaMar and Roche and has received honoraria for lectures from MSD, Lilly, Roche, Novartis, Pfizer, Exact Sciences, Daiichi Sankyo, Grünenthal, Gilead, AstraZeneca, and Eisai. He is editorial board member of *medactuell* from *medac*.

V. M. received speaker honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, GSK, Pfizer, MSD, Medac, Novartis, Roche, Teva, Seagen, Onkowieden, high5 Oncology, Medscape, Gilead. Consultancy honoraria from Hexal, Roche, Pierre Fabre, Amgen, ClinSol, Novartis, MSD, Daiichi Sankyo, Eisai, Lilly, Sanofi, Seagen, Gilead. Institutional research support from Novartis, Roche, Seagen, Genentech. Travel grants: Roche, Pfizer, Daiichi Sankyo.

E. S. received honoraria from Roche, Celgene, AstraZeneca, Novartis, Pfizer, Tesaro, Aurikamed GmbH, Pfizer, Seagen, Pierre Fabre, MCI Deutschland GmbH, bsh medical communications GmbH, Onkowieden TV.

A. S. received research grants from Celgene, Roche, honoraria from Amgen, AstraZeneca, Aurikamed, Bayer, Celgene, Clinsol, Connect-medica, Gilead, GSK, I-MED, Lilly, MCI Deutschland, Metaplan, MSD, Nanostring, Novartis, Onkowieden.de, Promedicis, Pfizer, Pierre Fabre, Roche, Seagen, Streamdup, Teva, Tesaro, Thieme and travel support from Celgene, Pfizer, Roche.

F. S. participated on advisory boards for Novartis, Lilly, Amgen and Roche and received honoraria for lectures from Roche, AstraZeneca, MSD, Novartis and Pfizer.

H. T. received honoraria from Novartis, Roche, Celgene, Teva, Pfizer, AstraZeneca and travel support from Roche, Celgene and Pfizer.

C. T. received honoraria for advisory boards and lectures from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Gilead, Lilly, MSD, Mylan, Nanostring, Novartis, Pfizer, Pierre Fabre, Puma, Roche, Seagen, Vifor.

M. T. has participated on advisory boards for AstraZeneca, Clovis, Daiichi Sankyo, Eisai, Gilead Science, GSK, Lilly, MSD, Novartis, Organon, Pfizer, Pierre Fabre, Seagen and Roche and has received honoraria for lectures from Amgen, Clovis, Daiichi Sankyo, Eisai, GSK, Lilly, MSD, Roche, Novartis, Organon, Pfizer, Seagen, Exact Sciences, Viatrix, Vifor and AstraZeneca and has received trial funding by Exact Sciences and Endomag Manuscript support was done by Amgen, ClearCut, pfm medical, Roche, Servier, Vifor.

M. U. all honoraria went to the institution/employer: Abbvie, Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Lilly, MSD, Myriad Genetics, Pfizer, Roche, Sanofi-Aventis, Novartis, Pierre Fabre, Seagen; Gilead.

M. W. has participated on advisory boards for AstraZeneca, Lilly, MSD, Novartis, Pfizer and Roche.

I. W. has participated on advisory boards for Novartis, Daiichi Sankyo, Lilly, Pfizer and received speaker honoraria from AstraZeneca, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche.

A. W. participated on advisory boards for Novartis, Lilly, Amgen, Pfizer, Roche, Tesaro, Eisai and received honoraria for lectures from Novartis, Pfizer, Aurikamed, Roche, Celgene.

R. W. has received honoraria, travel support from Agendia, Amgen, Aristo, AstraZeneca, Boehringer Ingelheim, Carl Zeiss, Meditec, Celgene, Daiichi Sankyo, Eisai, Exact Sciences, Genomic Health, Gilead, Glaxo Smith Kline, Hexal, Lilly, Medstrom Medical, MSD, Mundipharma, Mylan, Nanostring, Novartis, Odonate, Paxman, Palleos, Pfizer, Pierre Fabre, Puma Biotechnology, Riemser, Roche, Sandoz/Hexal, Sanofi, Genzyme, Seagen, Tesaro Bio, Teva, VeracYTE, Viatrix.

R. B. discloses advisory roles for AstraZeneca, Daiichi Sankyo, Eisai, Eli-Lilly, Gilead, Grünenthal, MSD, Novartis, Pfizer, Pierre Fabre, Puma, Roche, Seagen; lecture honoraria for AstraZeneca, Daiichi Sankyo, Eisai, Eli-Lilly, Gilead, Grünenthal, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen; research support for Daiichi Sankyo, MSD, Novartis, Roche.

C. K.-L. reports stock by Theraklion and Phaon Scientific (self and family), honoraria by Roche, AstraZeneca, Celgene, Novartis, Pfizer, Lilly, Hexal, Amgen, SonoScape (self) and Genomic Health, Amgen, AstraZeneca, Riemser, Carl Zeiss Meditec, Teva Pharmaceuticals Industries, Theraklion,

Janssen-Cilag, GlaxoSmithKline, LIV Pharma (family), Consulting to Roche, Novartis, Pfizer, Celgene, Phaon Scientific (self) and Pfizer, Novartis, SurgVision, Carl Zeiss Meditec, Amgen, Onkowieden (family); research funding by Roche, Novartis, Pfizer (self) as well as Travel and Accommodation by Roche, Daiichi Sankyo, Novartis (self) and Carl Zeiss Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo (family). J. E. has received consulting fees from AstraZeneca, Daiichi Sankyo, Pfizer, Novartis, Lilly, Pierre Fabre, Roche, and Tesaro; contracted research from Daiichi Sankyo, Pfizer, Lilly, Novartis, Seattle Genetics, AstraZeneca, Roche, and Odonate; and travel support from AstraZeneca, Daiichi Sankyo, Celgene, Pfizer, Novartis, Lilly, and Tesaro.

F.-A. T. has received honoraria from GSK, Hexal, MSD, Novartis, Pfizer, Roche and Tesaro and travel expenses from GSK.

The other authors have no conflict of interest to declare for this specific work.

## 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, Tolanev 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.22.0.0338
- [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] Tolanev 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](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 Patterns 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. Accessed June 26, 2022 at: [https://www.senologiekongress.de/xconfig/upload/files/Programme/Seno2022\\_Programm.pdf](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>